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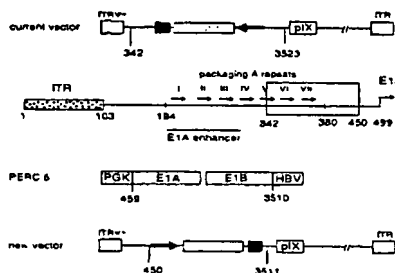
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60/233,180 15 September 2000 (15.09.2000) US(71) Applicant (for all designated States except US): MERCK
& CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway,
NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): EMINI, Emilio, A.
[US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-
0907 (US). YOUIL, Rima [AU/US]; 126 East Lincoln Av-
enue, Rahway, NJ 07065-0907 (US). BETT, Andrew, J.[CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-
0907 (US). CHEN, Ling [US/US]; 126 East Lincoln Av-
enue, Rahway, NJ 07065-0907 (US). KASLOW, David,
C. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-
0907 (US). SHIVER, John, W. [US/US]; 126 East Lincoln
Avenue, Rahway, NJ 07065-0907 (US). TONER, Timo-
thy, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US). CASIMIRO, Daniel, R. [PH/US]; 126
East Lincoln Avenue, Rahway, NJ 07065-0907 (US).(74) Common Representative: MERCK & CO., INC.; 126
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(54) Title: ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING CODON OPTIMIZED HIV1-GAG,
POL, NEF AND MODIFICATIONSModifications made to the current adenovector backbone in the generation of the new
vector.

(57) Abstract: First generation adenoviral vectors and associated recombinant adenovirus-based HIV vaccines which show enhanced stability and growth properties and greater cellular-mediated immunity are described within this specification. These adenoviral vectors are utilized to generate and produce through cell culture various adenoviral-based HIV-1 vaccines which contain HIV-1 gag, HIV-1 pol and/or HIV-1 nef polynucleotide pharmaceutical products, and biologically relevant modifications thereof. These adenovirus vaccines, when directly introduced into living vertebrate tissue, preferably a mammalian host such as a human or a non-human mammal of commercial or domestic veterinary importance, express the HIV1-Gag, Pol and/or Nef protein or biologically modification thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding HIV-1 Gag, encoding codon optimized HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The adenoviral vaccines of the present invention, when administered alone or in a combined modality regime, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.



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TITLE OF THE INVENTION

ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING
CODON OPTIMIZED HIV1-GAG, POL, NEF AND MODIFICATIONS

5 CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit, under 35 U.S.C. §119(e), of U.S.
provisional applications 60/233,180, 60/279,056, and Attorney Docket 20867PV2
(serial number unassigned), filed September 15, 2000, March 27, 2001, and
September 7, 2001, respectively.

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STATEMENT REGARDING FEDERALLY-SPONSORED R&D

Not Applicable

REFERENCE TO MICROFICHE APPENDIX

15

Not Applicable

FIELD OF THE INVENTION

The present invention relates to recombinant, replication-deficient first
generation adenovirus vaccines found to exhibit enhanced growth properties and
20 greater cellular-mediated immunity as compared to other replication-deficient vectors.
The invention also relates to the associated first generation adenoviral vectors
described herein, which, through the incorporation of additional 5' adenovirus
sequence, enhance large scale production efficiency of the recombinant, replication-
defective adenovirus described herein. Another aspect of the instant invention is the
25 surprising discovery that the intron A portion of the human cytomegalovirus (hCMV)
promoter constitutes a region of instability in adenoviral vector constructs. Removal
of this region from adenoviral expression constructs results in greatly improved vector
stability. Therefore, improved vectors expressing a transgene under the control of an
intron A-deleted CMV promoter constitute a further aspect of this invention. These
30 adenoviral vectors are useful for generating recombinant adenovirus vaccines against
human immunodeficiency virus (HIV). In particular, the first generation adenovirus
vectors disclosed herein are utilized to construct and generate adenovirus-based HIV-
1 vaccines which contain HIV-1 Gag, HIV-1 Pol and/or HIV-1 Nef polynucleotide
pharmaceutical products, and biologically active modifications thereof. Host
35 administration of the recombinant, replication-deficient adenovirus vaccines described
herein results in expression of HIV-1 Gag, HIV-1- Pol and/or Nef protein or

immunologically relevant modifications thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding codon optimized HIV-1 Gag, HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease,
5 reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef, and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The HIV adenovirus vaccines of the present invention, when administered alone or in a combined modality and/or prime/boost regimen, will offer a prophylactic
10 advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

BACKGROUND OF THE INVENTION

15 Human Immunodeficiency Virus-1 (HIV-1) is the etiological agent of acquired human immune deficiency syndrome (AIDS) and related disorders. HIV-1 is an RNA virus of the Retroviridae family and exhibits the 5' LTR-*gag-pol-env*-LTR 3' organization of all retroviruses. The integrated form of HIV-1, known as the provirus, is approximately 9.8 Kb in length. Each end of the viral genome contains
20 flanking sequences known as long terminal repeats (LTRs). The HIV genes encode at least nine proteins and are divided into three classes; the major structural proteins (Gag, Pol, and Env), the regulatory proteins (Tat and Rev); and the accessory proteins (Vpu, Vpr, Vif and Nef).

The *gag* gene encodes a 55-kilodalton (kDa) precursor protein (p55) which is
25 expressed from the unspliced viral mRNA and is proteolytically processed by the HIV protease, a product of the *pol* gene. The mature p55 protein products are p17 (matrix), p24 (capsid), p9 (nucleocapsid) and p6.

The *pol* gene encodes proteins necessary for virus replication; a reverse transcriptase, a protease, integrase and RNase H. These viral proteins are expressed
30 as a Gag-Pol fusion protein, a 160 kDa precursor protein which is generated via a ribosomal frame shifting. The viral encoded protease proteolytically cleaves the Pol polypeptide away from the Gag-Pol fusion and further cleaves the Pol polypeptide to the mature proteins which provide protease (Pro, P10), reverse transcriptase (RT, P50), integrase (IN, p31) and RNase H (RNase, p15) activities.

The *nef* gene encodes an early accessory HIV protein (Nef) which has been shown to possess several activities such as down regulating CD4 expression, disturbing T-cell activation and stimulating HIV infectivity.

The *env* gene encodes the viral envelope glycoprotein that is translated as a
5 160-kilodalton (kDa) precursor (gp160) and then cleaved by a cellular protease to yield the external 120-kDa envelope glycoprotein (gp120) and the transmembrane 41-kDa envelope glycoprotein (gp41). Gp120 and gp41 remain associated and are displayed on the viral particles and the surface of HIV-infected cells.

The *tat* gene encodes a long form and a short form of the Tat protein, a RNA
10 binding protein which is a transcriptional transactivator essential for HIV-1 replication.

The *rev* gene encodes the 13 kDa Rev protein, a RNA binding protein. The Rev protein binds to a region of the viral RNA termed the Rev response element (RRE). The Rev protein promotes transfer of unspliced viral RNA from the nucleus
15 to the cytoplasm. The Rev protein is required for HIV late gene expression and in turn, HIV replication.

Gp120 binds to the CD4/chemokine receptor present on the surface of helper T-lymphocytes, macrophages and other target cells in addition to other co-receptor molecules. X4 (macrophage tropic) virus show tropism for CD4/CXCR4 complexes
20 while a R5 (T-cell line tropic) virus interacts with a CD4/CCR5 receptor complex. After gp120 binds to CD4, gp41 mediates the fusion event responsible for virus entry. The virus fuses with and enters the target cell, followed by reverse transcription of its single stranded RNA genome into the double-stranded DNA via a RNA dependent DNA polymerase. The viral DNA, known as provirus, enters the cell nucleus, where
25 the viral DNA directs the production of new viral RNA within the nucleus, expression of early and late HIV viral proteins, and subsequently the production and cellular release of new virus particles. Recent advances in the ability to detect viral load within the host shows that the primary infection results in an extremely high generation and tissue distribution of the virus, followed by a steady state level of virus
30 (albeit through a continual viral production and turnover during this phase), leading ultimately to another burst of virus load which leads to the onset of clinical AIDS. Productively infected cells have a half life of several days, whereas chronically or latently infected cells have a 3-week half life, followed by non-productively infected cells which have a long half life (over 100 days) but do not significantly contribute to
35 day to day viral loads seen throughout the course of disease.

Destruction of CD4 helper T lymphocytes, which are critical to immune defense, is a major cause of the progressive immune dysfunction that is the hallmark of HIV infection. The loss of CD4 T-cells seriously impairs the body's ability to fight most invaders, but it has a particularly severe impact on the defenses against viruses, fungi, parasites and certain bacteria, including mycobacteria.

Effective treatment regimens for HIV-1 infected individuals have become available recently. However, these drugs will not have a significant impact on the disease in many parts of the world and they will have a minimal impact in halting the spread of infection within the human population. As is true of many other infectious diseases, a significant epidemiologic impact on the spread of HIV-1 infection will only occur subsequent to the development and introduction of an effective vaccine. There are a number of factors that have contributed to the lack of successful vaccine development to date. As noted above, it is now apparent that in a chronically infected person there exists constant virus production in spite of the presence of anti-HIV-1 humoral and cellular immune responses and destruction of virally infected cells. As in the case of other infectious diseases, the outcome of disease is the result of a balance between the kinetics and the magnitude of the immune response and the pathogen replicative rate and accessibility to the immune response. Pre-existing immunity may be more successful with an acute infection than an evolving immune response can be with an established infection. A second factor is the considerable genetic variability of the virus. Although anti-HIV-1 antibodies exist that can neutralize HIV-1 infectivity in cell culture, these antibodies are generally virus isolate-specific in their activity. It has proven impossible to define serological groupings of HIV-1 using traditional methods. Rather, the virus seems to define a serological "continuum" so that individual neutralizing antibody responses, at best, are effective against only a handful of viral variants. Given this latter observation, it would be useful to identify immunogens and related delivery technologies that are likely to elicit anti-HIV-1 cellular immune responses. It is known that in order to generate CTL responses antigen must be synthesized within or introduced into cells, subsequently processed into small peptides by the proteasome complex, and translocated into the endoplasmic reticulum/Golgi complex secretory pathway for eventual association with major histocompatibility complex (MHC) class I proteins. CD8⁺ T lymphocytes recognize antigen in association with class I MHC via the T cell receptor (TCR) and the CD8 cell surface protein. Activation of naive CD8⁺ T cells into activated effector or memory cells generally requires both TCR engagement of antigen as described above as well as engagement of costimulatory proteins. Optimal

induction of CTL responses usually requires "help" in the form of cytokines from CD4⁺ T lymphocytes which recognize antigen associated with MHC class II molecules via TCR and CD4 engagement.

European Patent Applications 0 638 316 (Published February 15, 1995) and 0
5 586 076 (Published March 9, 1994), (both assigned to American Home Products Corporation) describe replicating adenovirus vectors carrying an HIV gene, including *env* or *gag*. Various treatment regimens were used with chimpanzees and dogs, some of which included booster adenovirus or protein plus alum treatments.

Replication-defective adenoviral vectors harboring deletions in the E1 region
10 are known, and recent adenoviral vectors have incorporated the known packaging repeats into these vectors; e.g., see EP 0 707 071, disclosing, *inter alia*, an adenoviral vector deleted of E1 sequences from base pairs 459 to 3328; and U.S. Patent No. 6,033,908, disclosing, *inter alia*, an adenoviral vector deleted of base pairs 459-3510. The packaging efficiency of adenovirus has been taught to depend on the number of
15 incorporated individual A (packaging) repeats; see, e.g., Gräble and Hearing, 1990 *J. Virol.* 64(5):2047-2056; Gräble and Hearing, 1992 *J. Virol.* 66(2):723-731.

Larder, et al., (1987, *Nature* 327: 716-717) and Larder, et al., (1989, *Proc. Natl. Acad. Sci.* 86: 4803-4807) disclose site specific mutagenesis of HIV-1 RT and the effect such changes have on *in vitro* activity and infectivity related to interaction
20 with known inhibitors of RT.

Davies, et al. (1991, *Science* 252:, 88-95) disclose the crystal structure of the RNase H domain of HIV-1 Pol.

Schatz, et al. (1989, *FEBS Lett.* 257: 311-314) disclose that mutations Glu478Gln and His539Phe in a complete HIV-1 RT/RNase H DNA fragment results
25 in defective RNase activity without effecting RT activity.

Mizrahi, et al. (1990, *Nucl. Acids. Res.* 18: pp. 5359-5353) disclose additional mutations Asp443Asn and Asp498Asn in the RNase region of the *pol* gene which also results in defective RNase activity. The authors note that the Asp498Asn mutant was difficult to characterize due to instability of this mutant protein.

Leavitt, et al. (1993, *J. Biol. Chem.* 268: 2113-2119) disclose several
30 mutations, including a Asp64Val mutation, which show differing effect on HIV-1 integrase (IN) activity.

Wiskerchen, et al. (1995, *J. Virol.* 69: 376-386) disclose single and double mutants, including mutation of aspartic acid residues which effect HIV-1 IN and viral
35 replication functions.

It would be of great import in the battle against AIDS to produce a prophylactic- and/or therapeutic-based HIV vaccine which generates a strong cellular immune response against an HIV infection. The present invention addresses and meets these needs by disclosing a class of adenovirus vaccines which, upon host administration, express codon optimized and modified versions of the HIV-1 genes, *gag*, *pol* and *nef*. These recombinant, replication-defective adenovirus vaccines may be administered to a host, such as a human, alone or as part of a combined modality regimen and/or prime-boost vaccination regimen with components of the present invention and/or a distinct viral HIV DNA vaccine, non-viral HIV DNA vaccine, HIV subunit vaccine, an HIV whole killed vaccine and/or a live attenuated HIV vaccine.

SUMMARY OF THE INVENTION

The present invention relates to enhanced replication-defective recombinant adenovirus vaccine vectors and associated recombinant, replication-deficient adenovirus vaccines which encode various forms of HIV-1 Gag, HIV-1 Pol, and/or HIV-1 Nef, including immunologically relevant modifications of HIV-1 Gag, HIV-1 Pol and HIV-1 Nef. The adenovirus vaccines of the present invention express HIV antigens and provide for improved cellular-mediated immune responses upon host administration. Potential vaccinees include but are not limited to primates and especially humans and non-human primates, and also include any non-human mammal of commercial or domestic veterinary importance. An effect of the improved recombinant adenovirus-based vaccines of the present invention should be a lower transmission rate to previously uninfected individuals (i.e., prophylactic applications) and/or reduction in the levels of the viral loads within an infected individual (i.e., therapeutic applications), so as to prolong the asymptomatic phase of HIV-1 infection. In particular, the present invention relates to adenoviral-based vaccines which encode various forms of codon optimized HIV-1 Gag (including but in no way limited to p55 versions of codon optimized full length (FL) Gag and tPA-Gag fusion proteins), HIV-1 Pol, HIV-1 Nef, and selected modifications of immunological relevance. The administration, intracellular delivery and expression of these adenovirus vaccines elicit a host CTL and Th response. The preferred replication-defective recombinant adenoviral vaccine vectors include but are not limited to synthetic DNA molecules which (1) encode codon optimized versions of wild type HIV-1 Gag; (2) encode codon optimized versions of HIV-1 Pol; (3) encode codon optimized versions of HIV-1 Pol fusion proteins; (4) encode codon optimized versions of modified HIV-1 Pol proteins and fusion proteins, including but not limited

to *pol* modifications involving residues within the catalytic regions responsible for RT, RNase and IN activity within the host cell; (5) encode codon optimized versions of wild type HIV-1 Nef; (6) codon optimized versions of HIV-1 Nef fusion proteins; and/or (7) codon optimized versions of HIV-1 Nef derivatives, including but not limited to *nef* modifications involving introduction of an amino-terminal leader sequence, removal of an amino-terminal myristylation site and/or introduction of dileucine motif mutations. The Nef-based fusion and modified proteins, disclosed within this specification and expressed from an adenoviral-based vector vaccine this specification, may possess altered trafficking and/or host cell function while retaining the ability to be properly presented to the host MHC I complex and in turn elicit a host CTL and Th response. Examples of HIV-1 Gag, Pol and/or Nef fusion proteins include but are not limited to fusion of a leader or signal peptide at the NH₂-terminal portion of the viral antigen coding region. Such a leader peptide includes but is not limited to a tPA leader peptide.

The adenoviral vector utilized in construction of the HIV-1 Gag-, HIV-1 Pol- and/or HIV-1 Nef- based vaccines of the present invention may comprise any replication-defective adenoviral vector which provides for enhanced genetic stability of the recombinant adenoviral genome through large scale production and purification of the recombinant virus. In other words, an HIV-1 Gag-, Pol- or Nef-based adenovirus vaccine of the present invention is a purified recombinant, replication-defective adenovirus which is shown to be genetically stable through multiple passages in cell culture and remains so during large scale production and purification procedures. Such a recombinant adenovirus vector and harvested adenovirus vaccine lends itself to large scale dose filling and subsequent worldwide distribution procedures which will be demanded of an efficacious monovalent or multivalent HIV vaccine. The present invention meets this basic requirement with description of a replication-defective adenoviral vector and vectors derived therefrom, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 of the wildtype adenovirus genome. A preferred embodiment of the instant invention comprises base pairs 1-450 of a wildtype adenovirus. In other preferred embodiments, the replication-defective adenoviral vector has, in addition thereto, a region 3' to the E1-deleted region comprising base pairs 3511-3523. Basepairs 342-450 (more particularly, 400-450) constitute an extension of the 5' region of previously disclosed vectors carrying viral antigens, particularly HIV antigens (see, e.g., PCT International Application PCT/US00/18332, published

January 11, 2001 (WO 01/02067), which claims priority to U.S. Provisional Application Serial Nos. 60/142,631 and 60/148,981, filed 7/6/1999 and 8/13/1999, respectively; these documents herein incorporated by reference. Applicants have found that extending the 5' region further into the E1 gene into the disclosed vaccine
5 vectors incorporated elements found to be important in optimizing the packaging of the virus.

As compared to previous vectors not comprising basepairs from about 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 of the wildtype adenovirus genome, vectors comprising the above region exhibited enhanced
10 growth characteristics, with approximately 5-10 fold greater amplification rates, a more potent virus effect, allowing lower doses of virus to be used to generate equivalent immunity; and a greater cellular-mediated immune response than replication-deficient vectors not comprising this region (basepairs 1-450). Even more important, adenoviral constructs derived therefrom are very stable genetically in
15 large-scale production, particularly those comprising an expression cassette under the control of a hCMV promoter devoid of intron A. This is because Applicants have surprisingly found that the intron A portion of the hCMV promoter constituted a region of instability when employed in adenoviral vectors. Applicants have, therefore, identified an enhanced adenoviral vector which is particularly suited for use
20 in gene therapy and nucleotide-based vaccine vectors which, favorably, lends itself to large scale propagation.

A preferred embodiment of this invention is a replication-defective adenoviral vector in accordance with the above description wherein the gene is inserted in the form of a gene expression cassette comprising (a) a nucleic acid encoding a protein or
25 biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and, (c) a transcription terminator.

In preferred embodiments, the E1 gene, other than that contained within basepairs 1-450 or, alternatively, that contained within base pairs 1-450 and 3511-
30 3523 has been deleted from the adenoviral vector, and the gene expression cassette has replaced the deleted E1 gene. In other preferred embodiments, the replication defective adenovirus genome does not have a functional E3 gene, or the E3 gene has been deleted. Most preferably, the E3 region is present within the adenoviral genome. Further preferred embodiments are wherein the gene expression cassette is in an E1
35 anti-parallel (transcribed in a 3' to 5' direction relative to the vector backbone)

orientation or, more preferably, an E1 parallel (transcribed in a 5' to 3' direction relative to the vector backbone) orientation.

Further embodiments relate to a shuttle plasmid vector comprising: an adenoviral portion and a plasmid portion, wherein said adenovirus portion comprises:

- 5 a) a replication defective adenovirus genome, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 (preferably, 1-450) of the wildtype adenovirus genome and, preferably, in addition thereto, basepairs 3511-3523 of a wildtype adenovirus sequence; and b) a gene
10 expression cassette comprising: (a) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and (c) a transcription terminator and/or a polyadenylation site.

- Other aspects of this invention include a host cell comprising said adenoviral
15 vectors and/or said shuttle plasmid vectors; vaccine compositions comprising said vectors; and methods of producing the vectors comprising (a) introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and (b) harvesting the resultant adenoviral vectors.

- To this end, the present invention particularly relates to harvested
20 recombinant, replication defective virus derived from a host cell, such as but not limited to 293 cells or PER.C6[®] cells, including but not limited to harvested virus related to any of the MRKAd5 vector backbones, with or without an accompanying transgene, including but not limited to the HIV-1 antigens described herein. An HIV-1 vaccine is represented by any harvested, recombinant adenovirus material
25 which expresses any one or more of the HIV-1 antigens disclosed herein. This harvested material may then be purified, formulated and stored prior to host administration.

- Another aspect of this invention is a method of generating a cellular immune response against a protein in an individual comprising administering to the individual
30 an adenovirus vaccine vector comprising:

- a) a recombinant, replication defective adenoviral vector, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting adenovirus packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 (preferably, 1-450) and, preferably in addition thereto,
35 base pairs 3511-3523 of a wildtype adenovirus sequence, and,

b) a gene expression cassette comprising: (i) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (ii) a heterologous promoter operatively linked to the nucleic acid of part a); and (iii) a transcription terminator and/or a polyadenylation site.

5 In view of the efficacious nature of the adenoviral and/or DNA plasmid vaccines described herein, the present invention relates to all methodology regarding administration of one or more of these adenoviral and/or DNA plasmid vaccines to provide effective immunoprophylaxis, to prevent establishment of an HIV-1 infection following exposure to this virus, or as a post-HIV infection therapeutic vaccine to
10 mitigate the acute HIV-1 infection so as to result in the establishment of a lower virus load with beneficial long term consequences. As discussed herein, such a treatment regimen may include a monovalent or multivalent composition, various combined modality applications, and/or a prime/boost regimen to as to optimize antigen expression and a concomitant cellular-mediated and/or humoral immune response
15 upon inoculation into a living vertebrate tissue. Therefore, the present invention provides for methods of using the adenoviral and/or DNA plasmid vaccines disclosed herein within the various parameters disclosed herein as well as any additional parameters known in the art, which, upon introduction into mammalian tissue induces intracellular expression of the gag, pol and/or nef-based vaccines.

20 To this end, the present invention relates in part to methods of generating a cellular immune response in a vaccinee, preferably a human vaccinee, wherein the individual is given more than one administration of adenovirus vaccine vector, and it may be given in a regimen accompanied by the administration of a plasmid vaccine. The plasmid vaccine (also referred to herein as a "DNA plasmid vaccine" or "vaccine
25 plasmid" comprises a nucleic acid encoding a protein or an immunologically relevant portion thereof, a heterologous promoter operably linked to the nucleic acid sequence, and a transcription terminator or a polyadenylation signal (such as bGH or SPA, respectively). There may be a predetermined minimum amount of time separating the administrations. The individual can be given a first dose of plasmid vaccine, and then
30 a second dose of plasmid vaccine. Alternatively, the individual may be given a first dose of adenovirus vaccine, and then a second dose of adenovirus vaccine. In other embodiments, the plasmid vaccine is administered first, followed after a time by administration of the adenovirus vaccine. Conversely, the adenovirus vaccine may be administered first, followed by administration of plasmid vaccine after a time. In
35 these embodiments, an individual may be given multiple doses of the same adenovirus serotype in either viral vector or plasmid form, or the virus may be of

differing serotypes. In the alternative, a viral antigen of interest can be first delivered via a viral vaccine other than an adenovirus-based vaccine, and then followed with the adenoviral vaccine disclosed. Alternative viral vaccines include but are not limited to pox virus and venezuelan equine encephalitis virus.

5 The present invention also relates to multivalent adenovirus vaccine compositions which comprise Gag, Pol and Nef components described herein; see, e.g., Example 29 and Table 25. Such compositions will provide for an enhanced cellular immune response subsequent to host administration, particularly given the genetic diversity of human MHCs and of circulating virus. Examples, but not
10 limitations, include MRKAd5-vector based multivalent vaccine compositions which provide for a divalent (i.e., gag and nef, gag and pol, or pol and nef components) or a trivalent vaccine (i.e., gag, pol and nef components) composition. Such a multivalent vaccine may be filled for a single dose or may consist of multiple inoculations of each individually filled component; and may in addition be part of a prime/boost regimen
15 with viral or non-viral vector vaccines as introduced in the previous paragraph. To this end, preferred compositions are MRKAd5 adenovirus used in combination with multiple, distinct HIV antigen classes. Each HIV antigen class is subject to sequence manipulation, thus providing for a multitude of potential vaccine combinations; and such combinations are within the scope of the present invention. The utilization of
20 such combined modalities vaccine formulation and administration increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a single modality regimen.

 The concept of a "combined modality" as disclosed herein also covers the alternative mode of administration whereby multiple HIV-1 viral antigens may be
25 ligated into a proper shuttle plasmid for generation of a pre-adenoviral plasmid comprising multiple open reading frames. For example, a trivalent vector may comprise a gag-pol-nef fusion, in either a E3(-) or E3(+) background, preferably a E3 deleted backbone, or possibly a "2+1" divalent vaccine, such as a gag-pol fusion (i.e., codon optimized p55 gag and inactivated optimized pol; Example 29 and Table 25)
30 within the same MRKAd5 backbone, with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the two open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES). Therefore, a multivalent vaccine delivered as a single, or possibly a second
35 harvested recombinant, replication-deficient adenovirus is contemplated as part of the present invention.

Therefore, the adenoviral vaccines and plasmid DNA vaccines of this invention may be administered alone, or may be part of a prime and boost administration regimen. A mixed modality priming and booster inoculation scheme will result in an enhanced immune response, particularly if pre-existing anti-vector immune responses are present. This one aspect of this invention is a method of priming a subject with the plasmid vaccine by administering the plasmid vaccine at least one time, allowing a predetermined length of time to pass, and then boosting by administering the adenoviral vaccine. Multiple primings typically, 1-4, are usually employed, although more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. In experiments with rhesus monkeys, the animals were primed four times with plasmid vaccines, then were boosted 4 months later with the adenoviral vaccine. Their cellular immune response was notably higher than that of animals which had only received adenoviral vaccine. The use of a priming regimen may be particularly preferred in situations where a person has a pre-existing anti-adenovirus immune response.

It is an object of the present invention to provide for enhanced replication-defective recombinant adenoviral vaccine vector backbones. These recombinant adenoviral backbones may accept one or more transgenes, which may be passaged through cell culture for growth, amplification and harvest.

It is a further object to provide for enhanced replication-defective recombinant adenoviral vaccine vectors which encode various transgenes.

It is also an object of the present invention to provide for a harvested recombinant, replication-deficient adenovirus which shows enhanced growth and amplification rates while in combination with increased virus stability after continuous passage in cell culture. Such a recombinant adenovirus is particularly suited for use in gene therapy and nucleotide-based vaccine vectors which, favorably, lends itself to large scale propagation.

To this end, it is an object of the present invention to provide for (1) enhanced replication-defective recombinant adenoviral vaccine vectors as described herein which encode various forms of HIV-1 Gag, HIV-1 Pol, and/or HIV-1 Nef, including immunologically relevant modifications of HIV-1 Gag, HIV-1 Pol and HIV-1 Nef, and (2) harvested, purified recombinant replication-deficient adenovirus generated by passage of the adenoviral vectors of (1) through one or multiple passages through cell culture, including but not limited to passage through 293 cells or PER.C6® cells.

It is also an object of the present invention to provide for recombinant adenovirus harvested by one or multiple passages through cell culture. As relating to recombinant adenoviral vaccine vector, this recombinant virus is harvested and formulated for subsequent host administration.

5 It is also an object of the present invention to provide for replication-defective adenoviral vectors wherein at least one gene is inserted in the form of a gene expression cassette comprising (a) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and, (c) a transcription terminator.

10 It is also an object of the present invention to provide for a host cell comprising said adenoviral vectors and/or said shuttle plasmid vectors; vaccine compositions comprising said vectors; and methods of producing the vectors comprising (a) introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and (b) harvesting the resultant adenoviral vectors.

15 It is a further object of the present invention to provide for methods of generating a cellular immune response against a protein in an individual comprising administering to the individual an adenovirus vaccine vector comprising a) a replication defective adenoviral vector, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair 20 342 (more preferably, 400) to about 450 (preferably, 1-450) and, preferably, 3511-3523 of a wildtype adenovirus sequence, and, b) a gene expression cassette comprising: (i) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (ii) a heterologous promoter operatively linked to the nucleic acid of part a); and (iii) a transcription terminator and/or a 25 polyadenylation site.

It is also an object of the present invention to provide various alternatives for vaccine administration regimes, namely administration of one or more adenoviral and/or DNA plasmid vaccines described herein to provide effective immunoprophylaxis for uninfected individuals or a therapeutic treatment for HIV 30 infected patients. Such processes include but are not limited to multivalent HIV-1 vaccine compositions, various combined modality regimes as well as various prime/boost alternatives. These methods of administration, relating to vaccine composition and/or scheduled administration, will increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a 35 single modality regimen.

As used throughout the specification and claims, the following definitions and abbreviations are used:

"HAART" refers to -- highly active antiretroviral therapy --.

"first generation" vectors are characterized as being replication-defective.

5 They typically have a deleted or inactivated E1 gene region, and preferably have a deleted or inactivated E3 gene region as well.

"AEX" refers to Anion Exchange chromatography.

"QPA" refers to Quick PCR-based Potency Assay.

"bps" refers to basepairs.

10 "s" or "str" denotes that the transgene is in the E1 parallel or "straight" orientation.

"PBMCs" refers to peripheral blood monocyte cells.

"FL" refers to full length.

"FLgag" refers to a full-length optimized gag gene, as shown in Figure 2.

15 "Ad5-Flgag" refers to an adenovirus serotype 5 replication deficient virus which carries an expression cassette which comprises a full length optimized gag gene under the control of a CMV promoter.

"Promoter" means a recognition site on a DNA strand to which an RNA polymerase binds. The promoter forms an initiation complex with RNA polymerase
20 to initiate and drive transcriptional activity. The complex can be modified by activating sequences such as enhancers or inhibiting sequences such as silencers.

"Leader" means a DNA sequence at the 5' end of a structural gene which is transcribed along with the gene. This usually results a protein having an N-terminal peptide extension, often referred to as a pro-sequences.

25 "Intron" means a section of DNA occurring in the middle of a gene which does not code for an amino acid in the gene product. The precursor RNA of the intron is excised and is therefore not transcribed into mRNA not translated into protein.

"Immunologically relevant" or "biologically active" means (1) with regards to a viral protein, that the protein is capable, upon administration, of eliciting a
30 measurable immune response within an individual sufficient to retard the propagation and/or spread of the virus and/or to reduce the viral load present within the individual; or (2) with regards to a nucleotide sequence, that the sequence is capable of encoding for a protein capable of the above.

"Cassette" refers to a nucleic acid sequence which is to be expressed, along
35 with its transcription and translational control sequences. By changing the cassette, a vector can express a different sequence.

"bGHpA" refers to the bovine growth hormone transcription terminator/polyadenylation sequence.

"tPAgag" refers to a fusion between the leader sequence of the tissue plasminogen activator leader sequence and an optimized HIV gag gene, as
5 exemplified in Figure 30A-B, whether in a DNA or adenovirus-based vaccine vector.

Where utilized, "IA" or "inact" refers to an inactivated version of a gene (e.g. IApol).

"MCS" is "multiple cloning site".

In general, adenoviral constructs, gene constructs are named by reference to
10 the genes contained therein. For example:

"Ad5 HIV-1 gag", also referred to as the original HIV-1 gag adenoviral vector, is a vector containing a transgene cassette composed of a hCMV intron A promoter, the full length version of the human codon-optimized HIV-1 gag gene, and the bovine growth hormone polyadenylation signal. The transgene was inserted in the
15 E1 antiparallel orientation in an E1 and E3 deleted adenovector.

"MRK Ad5 HIV-1 gag" also referred to as "MRKAd5gag" or "Ad5gag2" is an adenoviral vector taught herein which is deleted of E1, comprises basepairs 1-450 and 3511-3523, and has a human codon-optimized HIV-1 gene in an E1 parallel orientation under the control of a CMV promoter without intron A. The construct
20 also comprises a bovine growth hormone polyadenylation signal.

"pV1JnsHIVgag", also referred to as "HIVFLgagPR9901", is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone.

25 "pV1JnsCMV(no intron)-FLgag-bGHpA" is a plasmid derived from pV1JnsHIVgag which is deleted of the intron A portion of CMV and which comprises the full length HIV gag gene. This plasmid is also referred to as "pV1JnsHIVgag-bGHpA", pV1Jns-hCMV-FL-gag-bGHpA" and "pV1JnsCMV(no intron) + FLgag + bGHpA".

30 "pV1JnsCMV(no intron)-FLgag-SPA" is a plasmid of the same composition as pV1JnsCMV(no intron)-FLgag-bGHpA except that the SPA termination sequence replaces that of bGHpA. This plasmid is also referred to as "pV1Jns-HIVgag-SPA" and pV1Jns-hCMV-FLgag-SPA".

35 "pdelE1sp1A" is a universal shuttle vector with no expression cassette (i.e., no promoter or polyA). The vector comprises wildtype adenovirus serotype 5 (Ad5) sequences from bp 1 to bp 341 and bp 3524 to bp 5798, and has a multiple cloning

site between the Ad5 sequences ending 341 bp and beginning 3524 bp. This plasmid is also referred to as the original Ad 5 shuttle vector.

"MRKpdelE1sp1A" or "MRKpdelE1(Pac/pIX/pack450)" or

"MRKpdelE1(Pac/pIX/pack450)Cla1" is a universal shuttle vector with no expression cassette (i.e. no promoter or polyA) comprising wildtype adenovirus serotype 5 (Ad5) sequences from bp1 to bp450 and bp 3511 to bp 5798. The vector has a multiple cloning site between the Ad5 sequence ending 450 bp and beginning 3511 bp. This shuttle vector may be used to insert the CMV promoter and the bGHpA fragments in both the straight ("str". or E1 parallel) orientation or in the opposite (opp. or E1 antiparallel) orientation)

"MRKpdelE1(Pac/pIX/pack450)+CMVmin+bGHpA(str.)" is still another shuttle vector which is the modified vector that contains the CMV promoter (no intronA) and the bGHpA fragments. The expression unit containing the hCMV promoter (no intron A) and the bovine growth hormone polyadenylation signal has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*III site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1/E3+)Cla1 pre-plasmid. This shuttle vector, as shown in Figures 22 and 23, was used to insert the respective IAPol and G2A,LLAA nef genes directly into.

"MRKpdelE1-CMV(no intron)-FLgag-bGHpA" is a shuttle comprising Ad5 sequences from basepairs 1-450 and 3511-5798, with an expression cassette containing human CMV without intron A, the full-length human codon-optimized HIV gag gene and bovine growth hormone polyadenylation signal. This plasmid is also referred to as "MRKpdelE1 shuttle +hCMV-FL-gag-BGHpA"

"MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA" is an adenoviral vector comprising all Ad5 sequences except those nucleotides encompassing the E1 region (from 451-3510), a human CMV promoter without intron A, a full-length human codon-optimized HIV gag gene, and a bovine growth hormone polyadenylation signal. This vector is also referred to as "MRKpAdHVE3 + hCMV-FL-gag-BGHpA", "MRKpAd5HIV-1gag", "MRKpAd5gag", "pMRKAd5gag" or "pAd5gag2".

"pV1Jns-HIV-pol inact(opt)" or "pV1Jns-HIV IA pol (opt)" is the inactivated Pol gene (contained within SEQ ID NO:3) cloned into the *Bgl*III site of V1Jns (Figure 17A-C). As noted herein, various derivatives of HIV-1 pol may be cloned into a plasmid expression vector such as V1Jns or V1Jns-tPA, thus serving directly as DNA vaccine candidates or as a source for subcloning into an appropriate adenoviral vector.

"MRKpdel+hCMVmin+FL-pol+bGHpA(s)" is the "MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.)" shuttle mentioned above which contains the IA pol gene is the proper orientation. This shuttle vector is used in a bacterial recombination with MRKpAd(E1-/E3+)Cla1.

5 "MRKpAd+hCMVmin+FL-pol+bGHpA(S)E3+", also referred to herein as "pMRKAd5pol", is the pre-adenovirus plasmid which comprises a CMV-pol inact(opt)-pGHpA construct. The construction of this pre-adenovirus plasmid is shown in Figure 22.

10 "pV1Jns/nef (G2A,LLAA)" or "V1Jns/opt nef (G2A,LLAA)" comprises codon optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175 (SEQ ID NO:13; which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662). This fragment is subcloned into the Bgl II site of V1Jns
15 and/or V1Jns-tPA (Figures 16A-B). As noted above for HIV-1 pol, HIV-1 nef constructs may be cloned into a plasmid expression vector such as V1Jns or V1Jns-tPA, thus serving directly as DNA vaccine candidates or as a source for subcloning into an appropriate adenoviral vector.

"MRKpdelE1hCMVminFL-nefBGHpA(s)", also referred to herein as
20 "pMRKAd5nef", is the pre-adenovirus plasmid which comprises a CMV-nef (G2A,LLAA) codon optimized sequence. The construction of this pre-adenovirus plasmid is shown in Figure 23.

BRIEF DESCRIPTION OF THE FIGURES

25 Figure 1 shows the original HIV-1 gag adenovector (Ad5HIV-1gag). This vector is disclosed in PCT International Application No. PCT/US00/18332 (WO 01/02607) filed July 3, 2000, claiming priority to U.S. Provisional Application Serial No. 60/142,631, filed July 6, 1999 and U.S. Application Serial No. 60/148,981, filed August 13, 1999, all three applications which are hereby incorporated by reference.

30 Figure 2 shows the nucleic acid sequence (SEQ ID NO: 29) of the optimized human HIV-1 gag open reading frame.

Figure 3 shows diagrammatically the new transgene constructs in comparison with the original gag transgene.

35 Figure 4 shows the modifications made to the original adenovector backbone in the generation of the novel vectors of the instant invention.

Figure 5 shows the virus mixing experiments that were carried out to determine the effects of the addition made to the packaging signal region (Expt. #1) and the E3 gene on viral growth (Expt. #2). The bars denote the region of modifications made to the E1 deletion.

5 Figure 6 shows an autoradiograph of viral DNA analysis following the viral mixing experiments described in Examples 6 and 7.

Figures 7A, 7B and 7C are as follows: Figure 7A shows the hCMV-Flgag-bGHpA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Both E1 parallel and E1 antiparallel transgene orientation are represented. Figure 7B shows the hCMV-Flgag-SPA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Again, both E1 parallel and E1 antiparallel transgene orientation are represented. Figure 7C shows the mCMV-Flgag-bGHpA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Once again, both E1 parallel and E1 antiparallel transgene orientation are represented.

Figure 8A shows the experiment designed to test the effect of transgene orientation.

Figure 8B shows the experiments designed to test the effect of polyadenylation signal.

20 Figure 9 shows viral DNA from the four adenoviral vectors tested (Example 12) at P5, following *Bst*E11 digestion.

Figure 10 shows viral DNA analysis of passages 11 and 12 of MRKpAdHVE3, MRKAd5HIV-1gag, and MRKAd5HIV-1gagE3-.

25 Figure 11 shows viral DNA analysis (*Hind*III digestion) of passage 6 MRKpAdHVE3 and MRKAd5HIV-1gag used to initiate the viral competition study. The last two lanes are passage 11 analysis of duplicate passages of the competition study (each virus at MOI of 280 viral particles).

30 Figure 12 shows viral DNA analysis by *Hind* III digestion on high passage numbers for MRKAd5HIV-1gag in serum-containing media with collections made at specified times. The first lane shows the 1kb DNA size marker. The other lanes represent pre-plasmid control (digested with *Pac*I and *Hind*III), MRKAd5HIV-1gag at P16, P19, and P21.

35 Figure 13 shows serum anti-p24 levels at 3 wks post i.m. immunization of balb/c mice (n=10) with varying doses of several Adgag constructs: (A) MRK Ad5 HIV-1 gag (through passage 5); (B) MRKAd5 hCMV-FLgag-bGHpA (E3-); (C) MRKAd5 hCMV-FLgag-SPA (E3+); (D) MRKAd5 mCMV-FLgag-bGHpA (E3+);

(E) research lot (293 cell-derived) of Ad5HIV-1 gag; and (F) clinical lot (Ad5gagFN0001) of Ad5HIV-1 gag. Reported are the geometric mean titers (GMT) for each cohort along with the standard error bars.

Figure 14 shows a restriction map of the pMRKAd5HIV-1gag vector.

5 Figures 15A-X illustrates the nucleotide sequence of the pMRKAd5HIV-1gag vector (SEQ ID NO:27.[coding] and SEQ ID NO:28 [non-coding]).

Figures 16A-B shows a schematic representation of DNA vaccine expression vectors V1Jns (A) and V1Jns-tPA (B), which are utilized for HIV-1 gag, pol and nef constructs in various DNA/viral vector combined modality regimens as disclosed

10 herein.

Figures 17A-C shows the nucleotide (SEQ ID NO:3) and amino acid sequence (SEQ ID NO:4) of IA-Pol. Underlined codons and amino acids denote mutations, as listed in Table 1.

15 Figure 18 shows codon optimized nucleotide and amino acid sequences through the fusion junction of tPA-pol inact(opt) (contained within SEQ ID NOs: 7 and 8, respectively). The underlined portion represents the NH₂-terminal region of IA-Pol.

20 Figures 19A-B show a nucleotide sequence comparison between wild type nef(jrfl) and codon optimized nef. The wild type nef gene from the jrfl isolate consists of 648 nucleotides capable of encoding a 216 amino acid polypeptide. WT, wild type sequence (SEQ ID NO:19); opt, codon-optimized sequence (contained within SEQ ID NO:1). The Nef amino acid sequence is shown in one-letter code (SEQ ID NO:2).

25 Figures 20A-C show nucleotide sequences at junctions between nef coding sequence and plasmid backbone of nef expression vectors V1Jns/nef (Figure 20A), V1Jns/nef(G2A,LLAA) (Figure 20B), V1Jns/tpanef (Figure 20C) and V1Jns/tpanef(LLAA) (Figure 20C, also). 5' and 3' flanking sequences of codon optimized nef or codon optimized nef mutant genes are indicated by bold/italic letters; nef and nef mutant coding sequences are indicated by plain letters. Also indicated (as
30 underlined) are the restriction endonuclease sites involved in construction of respective nef expression vectors. V1Jns/tpanef and V1Jns/tpanef(LLAA) have identical sequences at the junctions.

35 Figure 21 shows a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine 174 and 175 are the sites involved in myristylation and dileucine motif, respectively. For both versions of the tpanef fusion genes, the putative leader peptide cleavage sites are

indicated with “*”, and a exogenous serine residue introduced during the construction of the mutants is underlined.

Figure 22 shows diagrammatically the construction of the pre-adenovirus plasmid construct, MRKAd5Pol.

5 Figure 23 shows diagrammatically the construction of the pre-adenovirus plasmid construct, MRKAd5Nef.

Figure 24 shows a comparison of clade B vs. clade C anti-gag T cell responses in clade B HIV-infected subjects.

10 Figure 25 shows a comparison of clade B vs. clade C anti-nef T cell responses in clade B HIV-infected subjects.

Figures 26A-AO illustrates the nucleotide sequence of the pMRKAd5HIV-1pol adenoviral vector (SEQ ID NO:32 [coding] and SEQ ID NO:33 [non-coding]), comprising the coding region of the inactivated pol gene (SEQ ID NO3).

15 Figures 27A-AM illustrates the nucleotide sequence of the pMRKAd5HIV-1 nef adenoviral vector (SEQ ID NO:34 [coding] and SEQ ID NO:35 [non-coding]), comprising the coding region of the inactivated pol gene (SEQ ID NO13).

Figure 28 shows the stability of MRKAd5 vectors comprising various promoter fragments (hCMV or mCMV) and terminations signals (bGH or SPA) in E3(+) or E3(-) backbones.

20 Figures 29A and B shows the anion-exchange HPLC viral particle concentrations of the freeze-thaw recovered cell associated virus at the 24, 36, 48, and 60 hpi time points (Figure 29A) and the timcourse QPA supernatant titers (Figure 29B) for MRKAd5gag, MRKAd5pol and MRKAd5nef.

25 Figure 30 shows the nucleotide sequence (SEQ ID NO:36) and amino acid sequence (SEQ ID NO:37) comprising the open reading frame of a representative tPA-gag fusion for use in the DNA and/or adenoviral vaccine disclosed herein.

30 Figure 31 shows the intracellular γ IFN staining of PBMCs collected at week 10 (post DNA prime) and week 30 (post Ad boost). The cells were stimulated overnight in the presence or absence of the gag peptide pool. They were subsequently stained using fluorescence-tagged anti-CD3, anti-CD8, anti-CD4, and anti- γ IFN monoclonal antibodies. Each plot shows all CD3+ T cells which were segregated in terms of positive staining for surface CD8 and γ IFN production. The numbers in the upper right and lower right quadrants of each plot are the percentages of CD3+ cells that were CD8+ γ IFN+ and CD4+ γ IFN+, respectively.

35 Figure 32 shows a comparison of single-modality adenovirus immunization with DNA + adjuvant prime/adenovirus boost immunization.

Figures 33A-B show the nucleotide sequence (SEQ ID NO: 38) of the open reading frame for the gag-IAPol fusion of Example 29.

Figures 34A-B show the protein sequence (SEQ ID NO:39) of the gag-IAPol fusion frame.

5

DETAILED DESCRIPTION OF THE INVENTION

A novel replication-defective, or "first generation," adenoviral vector suitable for use in gene therapy or nucleotide-based vaccine vectors is described. This vector is at least partially deleted in E1 and comprises a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between about base pair 342 (more preferably, 400) to about 458 (preferably, 1-450) and, preferably, 3511-3523 of a wild-type adenovirus sequence. It has been found that a vector of this description possesses enhanced growth characteristics, with approximately 5-10 fold greater amplification rates, and is more potent allowing lower doses of virus to be used to generate equivalent immunity. The vector, furthermore, generates a harvested recombinant adenovirus which shows greater cellular-mediated immune responses than replication-deficient vectors not comprising this region (basepairs 342-450). Adenoviral constructs derived from these vectors are, further, very stable genetically, particularly those comprising a transgene under the control of a hCMV promoter devoid of intron A. Viruses in accordance with this description were passaged continually and analyzed; see Example 12. Each virus analyzed maintained its correct genetic structure. Analysis was also carried out under propagation conditions similar to that performed in large scale production. Again, the vectors were found to possess enhanced genetic stability; see Figure 12. Following 21 passages, the viral DNA showed no evidence of rearrangement, and was highly reproducible from one production lot to the next. The outcome of all relevant tests indicate that the adenoviral vector is extremely well suited for large-scale production of recombinant, replication-deficient adenovirus, as shown herein with the data associated with Figure 28.

A preferred adenoviral vector in accordance with this description is a vector comprising basepairs 1-450, which is deleted in E3. This vector can accommodate up to approximately 7,500 base pairs of foreign DNA inserts (or exogenous genetic material). Another preferred vector is one retaining E3 which comprises basepairs 1-450. A preferred vector of this description is an E3+ vector comprising basepairs 1-450 and 3511-3523. This vector, when deleted of the region spanning basepairs 451-3510, can accommodate up to approximately 4,850 base pairs of foreign DNA inserts

(or exogenous genetic material). The cloning capacities of the above vectors have been determined using 105% of the wildtype Ad5 sequence as the upper genome size limit.

Wildtype adenovirus serotype 5 is used as the basis for the specific basepair numbers provided throughout the specification. The wildtype adenovirus serotype 5 sequence is known and described in the art; *see*, Chroboczek *et al.*, 1992 *J. Virology* 186:280, which is hereby incorporated by reference. Accordingly, a particular embodiment of the instant invention is a vector based on the adenovirus serotype 5 sequence. One of skill in the art can readily identify the above regions in other adenovirus serotypes (e.g., serotypes 2, 4, 6, 12, 16, 17, 24, 31, 33, and 42), regions defined by basepairs corresponding to the above basepair positions given for adenovirus serotype 5. Accordingly, the instant invention encompasses all adenoviral vectors partially deleted in E1 comprising basepairs corresponding to 1-450 (particularly, 342-450) and, preferably, 3511-3523 of a wild-type adenovirus serotype 5 (Ad5) nucleic acid sequence. Particularly preferred embodiments of the instant invention are those derived from adenoviruses like Ad5 which are classified in subgroup C (e.g., Ad2).

Vectors in accordance with the instant invention are at least partially deleted in E1. Preferably the E1 region is completely deleted or inactivated. Most preferably, the region deleted of E1 is within basepairs 451-3510. It is to be noted that the extended 5' and 3' regions of the disclosed vectors are believed to effectively reduce the size of the E1 deletion of previous constructs without overlapping any part of the E1A/E1B gene present in the cell line used, i.e., the PER.C6[®] cell line transfected with base pairs 459-3510. Overlap of adenoviral sequences is avoided because of the possibility of recombination. One of ordinary skill in the art can certainly appreciate that the instant invention can, therefore, be modified if a different cell line transfected with a different segment of adenovirus DNA is utilized. For purposes of exemplification, a 5' region of base pairs 1 to up to 449 is more appropriate if a cell line is transfected with adenoviral sequence from base pairs 450-3510. This holds true as well in the consideration of segments 3' to the E1 deletion.

Preferred embodiments of the instant invention possess an intact E3 region (i.e., an E3 gene capable of encoding a functional E3). Alternate embodiments have a partially deleted E3, an inactivated E3 region, or a sequence completely deleted of E3. Applicants have found, in accordance with the instant invention, that virus comprising the E3 gene were able to amplify more rapidly compared with virus not comprising an E3 gene; see Figure 6 wherein a diagnostic CsCl band corresponding to the E3+ virus

tested (5,665 bp) was present in greater amount compared with the diagnostic band of 3,010 bp corresponding to the E3- virus. These results were obtained following a virus competition study involving mixing equal MOI ratio (1:1) of adenovectors both comprising the E3 gene and not comprising the E3 gene. This increased amplification capacity of the E3+ adenovectors was subsequently confirmed with growth studies; see Table 4A, wherein the E3+ virus exhibit amplification ratios of 470, 420 and 320 as compared with the 115 and 40-50 of the E3- constructs.

As stated above, vectors in accordance with the instant invention can accommodate up to approximately 4,850 base pairs of exogenous genetic material for an E3+ vector and approximately 7,500 base pairs for an E3- vector. Preferably, the insert brings the adenoviral vector as close as possible to a wild-type genomic size (e.g., for Ad5, 35,935 basepairs). It is well known that adenovirus amplifies best when they are close to their wild-type genomic size.

The genetic material can be inserted in an E1-parallel or an E1 anti-parallel orientation, as such is illustrated in Figure 7A, 7B, 7C and Figure 8A. Particularly preferred embodiments of the instant invention, have the insert in an E1-parallel orientation. Applicants have found, via competition experiments with plasmids containing transgenes in differing orientation (Figure 8A), that vector constructs with the foreign DNA insert in an E1-parallel orientation amplify better and actually out-compete E1-antiparallel-oriented transgenes. Viral DNA analysis of the mixtures at passage 3 and certainly at passage 6, showed a greater ratio of the virus carrying the transgene in the E1 parallel orientation as compared with the E1 anti-parallel version. By passage 10, the only viral species observed was the adenovector with the transgene in the E1 parallel orientation for both transgenes tested.

Adenoviral vectors in accordance with the instant invention are particularly well suited to effectuate expression of desired proteins, one example of which is an HIV protein, particularly an HIV full length gag protein. Exogenous genetic material encoding a protein of interest can exist in the form of an expression cassette. A gene expression cassette preferably comprises (a) a nucleic acid encoding a protein of interest; (b) a heterologous promoter operatively linked to the nucleic acid encoding the protein; and (c) a transcription terminator.

The transcriptional promoter is preferably recognized by an eukaryotic RNA polymerase. In a preferred embodiment, the promoter is a "strong" or "efficient" promoter. An example of a strong promoter is the immediate early human cytomegalovirus promoter (Chapman et al, 1991 *Nucl. Acids Res*19:3979-3986, which is incorporated by reference), preferably without intronic sequences. Most preferred

for use within the instant adenoviral vector is a human CMV promoter without intronic sequences, like intron A. Applicants have found that intron A, a portion of the human cytomegalovirus promoter (hCMV), constitutes a region of instability for adenoviral vectors. CMV without intron A has been found to effectuate (Examples 1-3) comparable expression capabilities *in vitro* when driving HIV gag expression and, furthermore, behaved equivalently to intron A-containing constructs in Balb/c mice *in vivo* with respect to their antibody and T-cell responses at both dosages of plasmid DNA tested (20 µg and 200 µg). Those skilled in the art will appreciate that any of a number of other known promoters, such as the strong immunoglobulin, or other eukaryotic gene promoters may also be used, including the EF1 alpha promoter, the murine CMV promoter, Rous sarcoma virus (RSV) promoter, SV40 early/late promoters and the beta-actin promoter.

In preferred embodiments, the promoter may also comprise a regulatable sequence such as the Tet operator sequence. This would be extremely useful, for example, in cases where the gene products are effecting a result other than that desired and repression is sought.

Preferred transcription termination sequences present within the gene expression cassette are the bovine growth hormone terminator/polyadenylation signal (bGHpA) and the short synthetic polyA signal (SPA) of 50 nucleotides in length, defined as follows: AATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGT-TTTTGTGTG (SEQ ID NO:26).

The combination of the CMV promoter (devoid of the intron A region) with the BGH terminator is particularly preferred although other promoter/terminator combinations in the context of FG adenovirus may also be used.

Other embodiments incorporate a leader or signal peptide into the transgene. A preferred leader is that from the tissue-specific plasminogen activator protein, tPA. Examples include but are not limited to the various tPA-gag, tPA-pol and tPA-nef adenovirus-based vaccines disclosed throughout this specification.

In view of the improved adenovirus vectors described herein, an essential portion of the present invention are adenoviral-based HIV vaccines comprising said adenovirus backbones which may be administered to a mammalian host, preferably a human host, in either a prophylactic or therapeutic setting. The HIV vaccines of the present invention, whether administered alone or in combination regimens with other viral- or non-viral-based DNA vaccines, should elicit potent and broad cellular immune responses against HIV that will either lessen the likelihood of persistent virus infection and/or lead to the establishment of a clinically significant lowered virus load

subject to HIV infection or in combination with HAART therapy, mitigate the effects of previously established HIV infection (antiviral immunotherapy(ARI)). While any HIV antigen (e.g., gag, pol, nef, gp160, gp41, gp120, tat, rev, etc.) may be utilized in the herein described recombinant adenoviral vectors, preferred embodiments include the codon optimized p55 gag antigen (herein exemplified as MRKAd5gag), pol and nef. Sequences based on different Clades of HIV-1 are suitable for use in the instant invention, most preferred of which are Clade B and Clade C. Particularly preferred embodiments are those sequences (especially, codon-optimized sequences) based on consensus Clade B sequences. Preferred versions of the MRKAd5pol and MRKAd5nef series of adenoviral vaccines will encode modified versions of pol or nef, as discussed herein. Preferred embodiments of the MRKAd5HIV-1 vectors carrying HIV envelope genes and modifications thereof comprise the HIV codon-optimized *env* sequences of PCT International Applications PCT/US97/02294 and PCT/US97/10517, published August 28, 1997 (WO 97/31115) and December 24, 1997, respectively; both documents of which are hereby incorporated by reference.

A most preferred aspect of the instant invention is the disclosed use of the adenoviral vector described above to effectuate expression of HIV gag. Sequences for many genes of many HIV strains are publicly available in GENBANK and primary, field isolates of HIV are available from the National Institute of Allergy and Infectious Diseases (NIAID) which has contracted with Quality Biological (Gaithersburg, MD) to make these strains available. Strains are also available from the World Health Organization (WHO), Geneva Switzerland. It is preferred that the gag gene be from an HIV-1 strain (CAM-1; Myers et al, eds. "Human Retroviruses and AIDS: 1995, IIA3-IIA19, which is hereby incorporated by reference). This gene closely resembles the consensus amino acid sequence for the clade B (North American/European) sequence. Therefore, it is within the purview of the skilled artisan to choose an appropriate nucleotide sequence which encodes a specific HIV gag antigen, or immunologically relevant portion thereof. As shown in Example 25, a clade B or clade C based p55 gag antigen will potentially be useful on a global scale. As noted herein, the transgene of choice for insertion in to a DNA or MRKAd-based adenoviral vector of the present invention is a codon optimized version of p55 gag. Such a MRKAd5gag adenoviral vector is documented in Example 11 and is at least referred to herein as MRKAd5HIV-1gag. Of course, additional versions are contemplated, including but not limited to modifications such as promoter (e.g., mCMV for hCMV) and/or pA-terminations signal (SPA for bGH) switching, as well as generating MRK Ad5 backbones with or without deletion of the Ad5 E3 gene.

The present invention also relates a series of MRKAd5pol-based adenoviral vaccines which are shown herein to generate cellular immune responses subsequent to administration in mice and non-human primate studies. Several of the MRKAd5pol series are exemplified herein. One such adenoviral vector is referred to as

5 MRKAd5hCMV-inact opt pol(E3+), which comprises the MRKAd5 backbone, the hCMV promoter (no intron A), an inactivated pol transgene, and contains the Ad5 E3 gene in the adenoviral backbone. A second exemplified pre-adenovirus plasmid and concomitant virus is referred to as MRKAd5hCMV-inact opt pol(E3-), which is identical to the former adenoviral vector except that the E3 is deleted. Both

10 constructions contain a codon optimized, inactivated version of HIV-1 Pol, wherein at least the entire coding region is disclosed herein as SEQ ID NO:3 and the expressed protein is shown as SEQ ID NO:4 (see also Figure 17A-C and Table 1, which show targeted deletion for inactivated pol. This and other preferred codon optimized versions of HIV Pol as disclosed herein are essentially as described in U.S.

15 Application Serial No. 09/745,221, filed December 21, 2000 and PCT International Application PCT/US00/34724, also filed December 21, 2000, both documents which are hereby incorporated by reference. As disclosed in the above-mentioned documents, the open reading frame for these codon-optimized HIV-1 Pol-based DNA vaccines are represented by codon optimized DNA molecules encoding codon

20 optimized HIV-1 Pol (e.g. SEQ ID NO:2), codon optimized HIV-1 Pol fused to an amino terminal localized leader sequence (e.g. SEQ ID NO:6), and especially preferable, and exemplified by the MRKAd5-Pol construct in e.g., Example 19, biologically inactivated pol ("inact opt Pol"; e.g., SEQ ID NO:4) which is devoid of significant PR, RT, RNase or IN activity associated with wild type Pol. In addition, a

25 construct related to SEQ ID NO:4 is contemplated which contains a leader peptide at the amino terminal region of the IA Pol protein. A specific construct is ligated within an appropriate DNA plasmid vector containing regulatory regions operatively linked to the respective HIV-1 Pol coding region, with or without a nucleotide sequence encoding a functional leader peptide. To this end, various HIV-1 Pol constructs

30 disclosed herein relate to open reading frames for cloning to the enhanced first generation Ad vectors of the present invention (such a series of MRKAd5pol adenoviral vaccine vectors), including but not limited to wild type Pol (comprising the DNA molecule encoding WT opt Pol, as set forth in SEQ ID NO:2), tPA-opt WTPol, (comprising the DNA molecule encoding tPA Pol, as set forth in SEQ ID NO:6), inact

35 opt Pol (comprising the DNA molecule encoding IA Pol, as set forth in SEQ ID NO:4), and tPA-inact opt Pol, (comprising the DNA molecule encoding tPA-inact opt

Pol, as set forth in SEQ ID NO:8). The pol-based versions of enhanced first generation adenovirus vaccines elicit CTL and Th cellular immune responses upon administration to the host, including primates and especially humans. As noted in the above, an effect of the cellular immune-directed vaccines of the present invention should be a lower transmission rate to previously uninfected individuals and/or reduction in the levels of the viral loads within an infected individual, so as to prolong the asymptomatic phase of HIV-1 infection.

The present invention further relates to a series of MRKAd5nef-based adenoviral vaccines which, similar to HIV gag and pol antigens, generate cellular immune responses subsequent to administration in mice and non-human primate studies. The MRKAd5nef series are exemplified herein by utilizing the improved MRK adenoviral backbone in combination with modified versions of HIV nef. These exemplified MRKAd5nef vectors are as follows: (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+), which comprises the improved MRKAd5 backbone, a human CMV promoter an intact Ad5 E3 gene and a modified nef gene: (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+), which is the same as (1) above but substituting a murine CMV promoter for a human CMV promoter; and (3) MRKAd5mCMV-tpanef(LLAA) (E3+), which is the same as (2) except that the nef transgene is tpanef(LLAA). Codon optimized versions of HIV-1 Nef and HIV-1 Nef modifications are essentially as described in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed December 15, 2000, both documents which are hereby incorporated by reference. Particular embodiments of codon optimized Nef and Nef modifications relate to a DNA molecule encoding HIV-1 Nef from the HIV-1 jf1 isolate wherein the codons are optimized for expression in a mammalian system such as a human. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:9, while the expressed open reading frame is disclosed herein as SEQ ID NO:10. Another embodiment of Nef-based coding regions for use in the adenoviral vectors of the present invention comprise a codon optimized DNA molecule encoding a protein containing the human plasminogen activator (tpa) leader peptide fused with the NH₂-terminus of the HIV-1 Nef polypeptide. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:11, while the expressed open reading frame is disclosed herein as SEQ ID NO:12. Another modified Nef optimized coding region relates to a DNA molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175, herein

described as opt nef (G2A, LLAA). The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:13, while the expressed open reading frame is disclosed herein as SEQ ID NO:14. MRKAd5nef vectors (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+) and (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+) contain this transgene. An additional embodiment relates to a DNA molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation site and dileucine motif have been deleted, as well as comprising a tPA leader peptide. This DNA molecule, opt tpanef (LLAA), comprises an open reading frame which encodes a Nef protein containing a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef (jfr1), wherein Leu-174 and Leu-175 are substituted with Ala-174 and Ala-175, herein referred to as opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, while the expressed open reading frame is disclosed herein as SEQ ID NO:16. The MRKAd5nef vector "MRKAd5mCMV-tpanef(LLAA) (E3+)" contains this transgene.

Along with the improved MRKAd5gag adenovirus vaccine vector described herein, generation of a MRKAd5pol and MRKAd5nef adenovirus vector provide for enhanced HIV vaccine capabilities. Namely, the generation of this trio of adenoviral vaccine vectors, all shown to generate effective cellular immune responses subsequent to host administration, provide for the ability to administer these vaccine candidates not only alone, but preferably as part of a divalent (i.e., gag and nef, gag and pol, or pol and nef components) or a trivalent vaccine (i.e., gag, pol and nef components). Therefore, a preferred aspect of the present invention are vaccine formulations and associated methods of administration and concomitant generation of host cellular immune responses associated with formulating three separate series of MRKAd5-based adenoviral vector vaccines. Of course, this MRKAd5 vaccine series based on distinct HIV antigens promotes expanded opportunities for formulation of a divalent or trivalent vaccine, or possibly administration of separate formulations of one or more monovalent or divalent formulations within a reasonable window of time. It is also within the scope of the present invention to embark on combined modality regimes which include multiple but distinct components from a specific antigen. An example, but certainly not a limitation, would be separate MRKAd5pol vectors, with one vaccine vector expressing wild type Pol (SEQ ID NO:2) and another MRKAd5pol vector expressing inactivated Pol (SEQ ID NO:6). Another example might be separate MRKAd5nef vectors, with one vaccine vector expressing the tPA/LLAA version of Nef (SEQ ID NO:16) and another MRKAd5nef vector expressing the G2A,LLAA modified version of Nef (SEQ ID NO:14). Therefore, the MRKAd5 adenoviral vectors of the present invention may be used in combination

with multiple, distinct HIV antigen classes. Each HIV antigen class is subject to sequence manipulation, thus providing for a multitude of potential vaccine combinations; and such combinations are within the scope of the present invention. The utilization of such combined modalities vaccine formulation and administration
5 increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a single modality regimen.

The present invention also relates to application of a mono-, dual-, or tri-modality administration regime of the MRKAd5gag, pol and nef adenoviral vaccine series in a prime/boost vaccination schedule. This prime/boost schedule may include
10 any reasonable combination of the MRKAd5gag, pol and nef adenoviral vaccine series disclosed herein. In addition, a prime/boost regime may also involve other viral and/or non-viral DNA vaccines. A preferable addition to an adenoviral vaccine vector regime includes but is not limited to plasmid DNA vaccines, especially DNA plasmid vaccines that contain at least one of the codon optimized gag, pol and nef
15 constructions, as disclosed herein.

Therefore, one aspect of this invention is the administration of the adenoviral vector containing the optimized gag gene in a prime/boost regimen in conjunction with a plasmid DNA encoding gag. To distinguish this plasmid from the adenoviral-containing shuttle plasmids used in the construction of an adenovirus vector, this
20 plasmid will be referred to as a "vaccine plasmid" or "DNA plasmid vaccine". Preferred vaccine plasmids for use in this administration protocol are disclosed in pending U.S. patent application 09/017,981, filed February 3, 1998 and WO98/34640, published August 13, 1998, both of which are hereby incorporated by reference. Briefly, the preferred vaccine plasmid is designated V1Jns-FLgag, which expresses
25 the same codon-optimized gag gene as the adenoviral vectors of this invention (see Figure 2 for the nucleotide sequence of the exemplified optimized codon version of full length p55 gag). The vaccine plasmid backbone, designated V1Jns contains the CMV immediate-early (IE) promoter and intron A, a bovine growth hormone-derived polyadenylation and transcription termination sequence as the gene expression
30 regulatory elements, and a minimal pUC backbone; see Montgomery *et al.*, 1993, *DNA Cell Biol.* 12:777-783. The pUC sequence permits high levels of plasmid production in *E. coli* and has a neomycin resistance gene in place of an ampicillin resistance gene to provide selected growth in the presence of kanamycin. Alternatively, a vaccine plasmid which has the CMV promoter deleted of intron A can
35 be used. Those of skill in the art will recognize that alternative vaccine plasmid

vectors may be easily substituted for these specific constructs, and this invention specifically envisions use of such alternative plasmid DNA vaccine vectors.

Another aspect of the present invention is a prime/boost regimen which includes a vaccine plasmid which encodes an HIV pol antigen, preferably a codon optimized form of pol and also preferably a vaccine plasmid which comprises a
5 nucleotide sequence which encodes a Pol antigen selected from the group of Pol antigens as shown in SEQ ID NOs: 2, 4, 6 and 8. The variety of potential DNA plasmid vaccines which encode various biologically active forms of HIV-1 Pol, wherein administration, intracellular delivery and expression of the HIV-1 Pol gene of
10 interest elicits a host CTL and Th response. The preferred synthetic DNA molecules of the present invention encode codon optimized wild type Pol (without Pro activity) and various codon optimized inactivated HIV-1 Pol proteins. The HIV-1 *pol* open reading disclosed herein are especially preferred for pharmaceutical uses, especially for human administration as delivered via a recombinant adenoviral vaccine,
15 especially an enhanced first generation recombinant adenoviral vaccine as described herein. Several embodiments of this portion of the invention are provided in detail below, namely DNA molecules which comprise a HIV-1 pol open reading frame, whether encoding full length pol or a modification or fusion as described herein, wherein the codon usage has been optimized for expression in a mammal, especially a
20 human. Again, these DNA sequences are positioned appropriately within a recombinant adenoviral vector, such as the exemplified recombinant adenoviral vector described herein, so as to promote expression of the respective HIV-1 Pol gene of interest, and subsequent to administration, elicit a host CTL and Th response. Again, these preferred, but in no way limiting, pol genes are as disclosed herein and
25 essentially as described in U.S. Application Serial No. 09/745,221, filed December 21, 2000 and PCT International Application PCT/US00/34724, also filed December 21, 2000, both documents which are hereby incorporated by reference.

A third series of vaccine plasmids which are useful in a combined modality and/or prime/boost regimen are vaccine plasmids which encode an HIV nef antigen or
30 biologically and/or immunologically relevant modification thereof. As noted elsewhere, preferred vaccine plasmids contain a codon optimized form of nef and also preferably comprise a nucleotide sequence which encodes a Nef antigen selected from the group of Nef antigens as shown in SEQ ID NOs: 10, 12, 14 and 16. These preferred nef coding regions are disclosed herein, as well as being described in U.S.
35 Application Serial No. 09/738,782, filed December 15, 2000 and PCT International

Application PCT/US00/34162, also filed December 15, 2000, both documents which are hereby incorporated by reference.

Therefore, the adenoviral vaccines and plasmid DNA vaccines of this invention may be administered alone, or may be part of a prime and boost
5 administration regimen. A mixed modality priming and booster inoculation scheme will result in an enhanced immune response, particularly if pre-existing anti-vector immune responses are present. This one aspect of this invention is a method of priming a subject with the plasmid vaccine by administering the plasmid vaccine at
10 least one time, allowing a predetermined length of time to pass, and then boosting by administering the adenoviral vaccine. Multiple primings typically, 1-4, are usually employed, although more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. In experiments with rhesus monkeys, the animals were primed four times with plasmid vaccines, then were boosted 4 months later with the adenoviral vaccine.
15 Their cellular immune response was notably higher than that of animals which had only received adenoviral vaccine. The use of a priming regimen may be particularly preferred in situations where a person has a pre-existing anti-adenovirus immune response.

Furthermore and in the alternative, multiple HIV-1 viral antigens, such as the
20 MRKAd5 adenoviral vaccines disclosed herein, may be ligated into a proper shuttle plasmid for generation of a pre-adenoviral plasmid comprising multiple open reading frames. For example a trivalent vector may comprise a gag-pol-nef fusion, in either a E3(-) or E3(+) background, preferably a E3 deleted backbone, or possibly a "2+1" divalent vaccine, such as a gag-pol fusion (i.e., codon optimized p55 gag and
25 inactivated optimized pol; Example 29 and Table 25) within the same MRKAd5 backbone, with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the two open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES), as disclosed in
30 International Publication No. WO 95/24485, which is hereby incorporated by reference. Figure 9 shows that the use of multiple promoters and termination sequences provide for similar growth properties, while Figure 28 shows that these MRKAd5gag-based vectors are also stable at least through passage 21. In the absence of the use of IRES-based technology, it is preferred that a distinct promoter be used to
35 support each respective open reading frame, so as to best preserve vector stability. As examples, and certainly not as limitations, potential multiple transgene vaccines may

include a three transgene vector such as hCMV-gagpol-bGHpA + mCMV-nef-SPA in an E3 deleted backbone or hCMV-gagpol-bGHpA + mCMV-nef-SPA(E3+).

Potential "2+1" divalent vaccines of the present invention might be a hCMV-gag-bGHpA + mCMV-nef-SPA in an E3+ backbone (vector #1) in combination with

5 hCMV-pol-bGHpA in an E3+ backbone (vector #2), with all transgenes in the E1 parallel orientation. Fusion constructs other than the gag-pol fusion described above are also suitable for use in various divalent vaccine strategies and can be composed of any two HIV antigens fused to one another (*e.g.*, nef-pol and gag-nef). These adenoviral compositions are, as above, preferably delivered along with an adenoviral
10 composition comprising an additional HIV antigen in order to diversify the immune response generated upon administration. Therefore, a multivalent vaccine delivered in a single, or possible second, adenoviral vector is certainly contemplated as part of the present invention. Again, this mode of administration is another example of whereby an efficacious adenovirus-based HIV-1 vaccine may be administered via a
15 combined modality regime. It is important to note, however, that in terms of deciding on an insert for the disclosed adenoviral vectors, due consideration must be dedicated to the effective packaging limitations of the adenovirus vehicle. Adenovirus has been shown to exhibit an upper cloning capacity limit of approximately 105% of the wildtype Ad5 sequence.

20 Regardless of the gene chosen for expression, it is preferred that the sequence be "optimized" for expression in a human cellular environment. A "triplet" codon of four possible nucleotide bases can exist in 64 variant forms. That these forms provide the message for only 20 different amino acids (as well as transcription initiation and termination) means that some amino acids can be coded for by more than one codon.
25 Indeed, some amino acids have as many as six "redundant", alternative codons while some others have a single, required codon. For reasons not completely understood, alternative codons are not at all uniformly present in the endogenous DNA of differing types of cells and there appears to exist variable natural hierarchy or "preference" for certain codons in certain types of cells. As one example, the amino
30 acid leucine is specified by any of six DNA codons including CTA, CTC, CTG, CTT, TTA, and TTG (which correspond, respectively, to the mRNA codons, CUA, CUC, CUG, CUU, UUA and UUG). Exhaustive analysis of genome codon frequencies for microorganisms has revealed endogenous DNA of *E. coli* most commonly contains the CTG leucine-specifying codon, while the DNA of yeasts and slime molds most
35 commonly includes a TTA leucine-specifying codon. In view of this hierarchy, it is generally held that the likelihood of obtaining high levels of expression of a leucine-

rich polypeptide by an *E. coli* host will depend to some extent on the frequency of codon use. For example, a gene rich in TTA codons will in all probability be poorly expressed in *E. coli*, whereas a CTG rich gene will probably highly express the polypeptide. Similarly, when yeast cells are the projected transformation host cells
5 for expression of a leucine-rich polypeptide, a preferred codon for use in an inserted DNA would be TTA.

The implications of codon preference phenomena on recombinant DNA techniques are manifest, and the phenomenon may serve to explain many prior failures to achieve high expression levels of exogenous genes in successfully
10 transformed host organisms--a less "preferred" codon may be repeatedly present in the inserted gene and the host cell machinery for expression may not operate as efficiently. This phenomenon suggests that synthetic genes which have been designed to include a projected host cell's preferred codons provide a preferred form of foreign genetic material for practice of recombinant DNA techniques. Thus, one aspect of
15 this invention is an adenovirus vector or adenovirus vector in some combination with a vaccine plasmid where both specifically include a gene which is codon optimized for expression in a human cellular environment. As noted herein, a preferred gene for use in the instant invention is a codon-optimized HIV gene and, particularly, HIV gag, pol or nef.

20 Adenoviral vectors in accordance with the instant invention can be constructed using known techniques, such as those reviewed in Hitt et al, 1997 "Human Adenovirus Vectors for Gene Transfer into Mammalian Cells" *Advances in Pharmacology* 40:137-206, which is hereby incorporated by reference.

In constructing the adenoviral vectors of this invention, it is often convenient
25 to insert them into a plasmid or shuttle vector. These techniques are known and described in Hitt et al., *supra*. This invention specifically includes both the adenovirus and the adenovirus when inserted into a shuttle plasmid.

Preferred shuttle vectors contain an adenoviral portion and a plasmid portion. The adenoviral portion is essentially the same as the adenovirus vector discussed
30 *supra*, containing adenoviral sequences (with non-functional or deleted E1 and E3 regions) and the gene expression cassette, flanked by convenient restriction sites. The plasmid portion of the shuttle vector often contains an antibiotic resistance marker under transcriptional control of a prokaryotic promoter so that expression of the antibiotic does not occur in eukaryotic cells. Ampicillin resistance genes, neomycin
35 resistance genes and other pharmaceutically acceptable antibiotic resistance markers may be used. To aid in the high level production of the polynucleotide by

fermentation in prokaryotic organisms, it is advantageous for the shuttle vector to contain a prokaryotic origin of replication and be of high copy number. A number of commercially available prokaryotic cloning vectors provide these benefits. It is desirable to remove non-essential DNA sequences. It is also desirable that the vectors
5 not be able to replicate in eukaryotic cells. This minimizes the risk of integration of polynucleotide vaccine sequences into the recipients' genome. Tissue-specific promoters or enhancers may be used whenever it is desirable to limit expression of the polynucleotide to a particular tissue type.

In one embodiment of this invention, the pre-plasmids (e.g., pMRKAd5pol,
10 pMRKAd5nef and pMRKAd5gag were generated by homologous recombination using the MRKHVE3 (and MRKHVO for the E3- version) backbones and the appropriate shuttle vector, as shown for pMRKAd5pol in Figure 22 and for pMRKAd5nef in Figure 23. The plasmid in linear form is capable of replication after entering the PER.C6[®] cells and virus is produced. The infected cells and media were
15 harvested after viral replication was complete.

Viral vectors can be propagated in various E1 complementing cell lines, including the known cell lines 293 and PER.C6[®]. Both these cell lines express the adenoviral E1 gene product. PER.C6[®] is described in WO 97/00326 (published January 3, 1997) and issued U.S. Patent No. 6,033,908, both of which are hereby
20 incorporated by reference. It is a primary human retinoblast cell line transduced with an E1 gene segment that complements the production of replication deficient (FG) adenovirus, but is designed to prevent generation of replication competent adenovirus by homologous recombination. Cells of particular interest have been stably transformed with a transgene that encodes the AD5E1A and E1B gene, like PER.C6[®],
25 from 459 bp to 3510 bp inclusive. 293 cells are described in Graham et al., 1977 *J. Gen. Virol* 36:59-72, which is hereby incorporated by reference. As stated above, consideration must be given to the adenoviral sequences present in the complementing cell line used. It is important that the sequences not overlap with that present in the vector if the possibility of recombination is to be minimized.

30 It has been found that vectors generated in accordance with the above description are more effective in inducing an immune response and, thus, constitute very promising vaccine candidates. More particularly, it has been found that first generation adenoviral vectors in accordance with the above description carrying a codon-optimized HIV gag gene, regulated with a strong heterologous promoter can be
35 used as human anti-HIV vaccines, and are capable of inducing immune responses.

Standard techniques of molecular biology for preparing and purifying DNA constructs enable the preparation of the DNA immunogens of this invention.

A vaccine composition comprising an adenoviral vector in accordance with the instant invention may contain physiologically acceptable components, such as
5 buffer, normal saline or phosphate buffered saline, sucrose, other salts and polysorbate. One preferred formulation has: 2.5-10 mM TRIS buffer, preferably about 5 mM TRIS buffer; 25-100 mM NaCl, preferably about 75 mM NaCl; 2.5-10% sucrose, preferably about 5% sucrose; 0.01 -2 mM MgCl₂; and 0.001%-0.01% polysorbate 80 (plant derived). The pH should range from about 7.0-9.0, preferably
10 about 8.0. One skilled in the art will appreciate that other conventional vaccine excipients may also be used it make the formulation. The preferred formulation contains 5mM TRIS, 75 mM NaCl, 5% sucrose, 1mM MgCl₂, 0.005% polysorbate 80 at pH 8.0 This has a pH and divalent cation composition which is near the optimum for Ad5 stability and minimizes the potential for adsorption of virus to a glass surface.
15 It does not cause tissue irritation upon intramuscular injection. It is preferably frozen until use.

The amount of adenoviral particles in the vaccine composition to be introduced into a vaccine recipient will depend on the strength of the transcriptional and translational promoters used and on the immunogenicity of the expressed gene
20 product. In general, an immunologically or prophylactically effective dose of 1×10^7 to 1×10^{12} particles and preferably about 1×10^{10} to 1×10^{11} particles is administered directly into muscle tissue. Subcutaneous injection, intradermal introduction, impression through the skin, and other modes of administration such as intraperitoneal, intravenous, or inhalation delivery are also contemplated. It is also
25 contemplated that booster vaccinations are to be provided. Following vaccination with HIV adenoviral vector, boosting with a subsequent HIV adenoviral vector and/or plasmid may be desirable. Parenteral administration, such as intravenous, intramuscular, subcutaneous or other means of administration of interleukin-12 protein, concurrently with or subsequent to parenteral introduction of the vaccine
30 compositions of this invention is also advantageous.

The adenoviral vector and/or vaccine plasmids of this invention polynucleotide may be unassociated with any proteins, adjuvants or other agents which impact on the recipients' immune system. In this case, it is desirable for the vector to be in a physiologically acceptable solution, such as, but not limited to, sterile
35 saline or sterile buffered saline. Alternatively, the vector may be associated with an adjuvant known in the art to boost immune responses (i.e., a "biologically effective"

adjuvant), such as a protein or other carrier. Vaccine plasmids of this invention may, for instance, be delivered in saline (e.g., PBS) with or without an adjuvant. Preferred adjuvants are Alum or CRL1005 Block Copolymer. Agents which assist in the cellular uptake of DNA, such as, but not limited to, calcium ions, may also be used to advantage. These agents are generally referred to herein as transfection facilitating reagents and pharmaceutically acceptable carriers. Techniques for coating microprojectiles coated with polynucleotide are known in the art and are also useful in connection with this invention.

This invention also includes a prime and boost regimen wherein a first adenoviral vector is administered, then a booster dose is given. The booster dose may be repeated at selected time intervals. Alternatively, a preferred inoculation scheme comprises priming with a first adenovirus serotype and then boosting with a second adenovirus serotype. More preferably, the inoculation scheme comprises priming with a first adenovirus serotype and then boosting with a second adenovirus serotype, wherein the first and second adenovirus serotypes are classified within separate subgroups of adenoviruses. The above prime/boost schemes are particularly preferred in those situations where a preexisting immunity is identified to the adenoviral vector of choice. In this type of scheme, the individual or population of individuals is primed with an adenovirus of a serotype other than that to which the preexisting immunity is identified. This enables the first adenovirus to effectuate sufficient expression of the transgene while evading existing immunity to the second adenovirus (the boosting adenovirus) and, further, allows for the subsequent delivery of the transgene via the boosting adenovirus to be more effective. Adenovirus serotype 5 is one example of a virus to which such a scheme might be desirable. In accordance with this invention, therefore, one might decide to prime with a non-group C adenovirus (e.g., Ad12, a group A adenovirus, Ad24, a group D adenovirus, or Ad35, a group B adenovirus) to evade anti-Ad5 immunity and then boost with Ad5, a group C adenovirus. Another preferred embodiment involves administration of a different adenovirus (including non-human adenovirus) vaccine followed by administration of the adenoviral vaccines disclosed. In the alternative, a viral antigen of interest can be first delivered via a viral vaccine other than an adenovirus-based vaccine, and then followed with the adenoviral vaccine disclosed. Alternative viral vaccines include but are not limited to pox virus and venezuelan equine encephalitis virus.

A large body of human and animal data supports the importance of cellular immune responses, especially CTL in controlling (or eliminating) HIV infection. In humans, very high levels of CTL develop following primary infection and correlate

with the control of viremia. Several small groups of individuals have been described who are repeatedly exposed to HIV by remain uninfected; CTL has been noted in several of these cohorts. In the SIV model of HIV infection, CTL similarly develops following primary infection, and it has been demonstrated that addition of anti-CD8
5 monoclonal antibody abrogated this control of infection and leads to disease progression. This invention uses adenoviral vaccines alone or in combination with plasmid vaccines to induce CTL.

The following non-limiting Examples are presented to better illustrate the invention.

10

EXAMPLE 1

Removal of the Intron A Portion of the hCMV Promoter

GMP grade pVIJnsHIVgag was used as the starting material to amplify the hCMV promoter. PVIJnsHIVgag is a plasmid comprising the CMV immediate-early
15 (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone; see Montgomery *et al.*, *supra* for a description of the plasmid backbone. The amplification was performed with primers suitably positioned to flank the hCMV promoter. A 5' primer was placed upstream of the *MscI* site of
20 the hCMV promoter and a 3' primer (designed to contain the *BglII* recognition sequence) was placed 3' of the hCMV promoter. The resulting PCR product (using high fidelity *Taq* polymerase) which encompassed the entire hCMV promoter (minus intron A) was cloned into TOPO PCR blunt vector and then removed by double digestion with *MscI* and *BglII*. This fragment was then cloned back into the original
25 GMP grade pV1JnsHIVgag plasmid from which the original promoter, intron A, and the gag gene were removed following *MscI* and *BglII* digestion. This ligation reaction resulted in the construction of a hCMV promoter (minus intron A) + bGHpA expression cassette within the original pV1JnsHIVgag vector backbone. This vector is designated pVIJnsCMV(no intron).

30 The FLgag gene was excised from pV1JnsHIVgag using *BglII* digestion and the 1,526 bp gene was gel purified and cloned into pV1JnsCMV(no intron) at the *BglII* site. Colonies were screened using *SmaI* restriction enzymes to identify clones that carried the FLgag gene in the correct orientation. This plasmid, designated pV1JnsCMV(no intron)-FLgag-bGHpA, was fully sequenced to confirm sequence
35 integrity.

Two additional transgenes were also constructed. The plasmid, pV1JnsCMV(no intron)-FLgag-SPA, is identical to pV1JnsCMV(no intron)-FLgag-bGHpA except that the bovine growth hormone polyadenylation signal has been replaced with a short synthetic polyA signal (SPA) of 50 nucleotides in length. The sequence of the SPA is as shown, with the essential components (poly(A) site, (GT)_n, and (T)_n; respectively) underlined:

AATAAAAGATCTTTATTTTCATTAGATCTGTGTG TTGGTTTTTTGTGTG
(SEQ ID NO:18).

The plasmid, pV1Jns-mCMV-FLgag-bGHpA, is identical to the pV1JnsCMV(no intron)-FLgag-bGHpA except that the hCMV promoter has been removed and replaced with the murine CMV (mCMV) promoter.

Figure 3 diagrammatically shows the new transgene constructs in comparison with the original transgene.

EXAMPLE 2

Gag Expression Assay for Modified Gag Transgenes

Gag Elisa was performed on culture supernatants obtained from transient tissue culture transfection experiments in which the two new hCMV-containing plasmid constructs, pV1JnsCMV(no intron)-FLgag-bGHpA and pV1JnsCMV(no intron)-FLgag-SPA, both devoid of intron A, were compared to pV1JnsHIVgag which, as noted above possesses the intron A as part of the hCMV promoter. Table 2 below shows the *in vitro* gag expression data of the new gag plasmids compared with the GMP grade original plasmid. The results displayed in Table 2 show that both of the new hCMV gag plasmid constructs have expression capacities comparable to the original plasmid construct which contains the intron A portion of the hCMV promoter.

Table 2: *In vitro* DNA transfection of original and new plasmid HIV-1 gag constructs.

Plasmid	$\mu\text{g gag}/10^6 \text{ COS cells}/5\mu\text{g DNA}/48 \text{ hr}$
HIVFL-gagPR9901 ^a	10.8
PV1Jns-hCMV-FLgag-bGHpA ^b	16.6
pV1Jns-hCMV-FLgag-SPA ^{b,c}	12.0

^a GMP grade pV1Jns-hCMVintronA-FLgag-bGHpA.

5 ^b New plasmid constructions that have the intron A portion removed from the hCMV promoter.

^c In this construct the bGH terminator has been replaced with the short synthetic polyadenylation signal (SPA)

10

EXAMPLE 3

Rodent (Balb/c) Study for Modified gag Transgenes

A rodent study was performed on the two new plasmid constructs described above – pV1JnsCMV(no intron)-FLgag-bGHpA and pV1JnsCMV(no intron)-FLgag-SPA - in order to compare them with the construct described above
 15 possessing the intron A portion of the CMV promoter, pV1JnsHIVgag. Gag antibody and Elispot responses (described in PCT International Application No. PCT/US00/18332 (WO 01/02607) filed July 3, 2000, claiming priority to U.S. Provisional Application Serial No. 60/142,631, filed July 6, 1999 and U.S. Application Serial No. 60/148,981, filed August 13, 1999, all three applications which
 20 are hereby incorporated by reference) were measured. The results displayed in Table 3 below, show that the new plasmid constructs behaved equivalently to the original construct in Balb/c mice with respect to their antibody and T-cell responses at both dosages of plasmid DNA tested, 20 μg and 200 μg .

EXAMPLE 4

Table 3: HIV191: Immunogenicity of V1Jns-gag under different promoter and termination control elements.

DNA ^a Promoter/terminator	Dose, ug ^b	Anti-p24 Titers (3 Wk PD1) ^c			SFC/10 ⁶ Cells (4 Wk PD1) ^d		
		GMT	+SE	-SE	Media	gag197-205	p24
HIVFL-gagPR9901 (GMP grade)	200	12800	4652	3412	2(2)	129(19)	30(11)
	20	5572	1574	1227	0	56(9)	25(6)
pV1Jns-hCMV- FL-gag-bGHpA	200	11143	2831	2257	0	98(5)	12(6)
	20	7352	2808	2032	0	73(9)	11(6)
pV1Jns-hCMV- FL-gag-SPA	200	16890	5815	4326	1(1)	94(4)	26(7)
	20	5971	5361	2825	0	85(17)	38(10)
Naïve	0	123	50	36	0	0	0

^ain PBS^bl.m. Injections into both quads, 50 µL per quad^cn=10; GMT, geometric mean titer; SE, standard. error^dn=5, pooled spleens; mean of triplicate wells and standard. deviation. in parentheses;

Construction of the Modified Shuttle Vector -"MRKpdelE1 Shuttle"

The modifications to the original Ad5 shuttle vector (pdelE1sp1A; a vector comprising Ad5 sequences from basepairs 1-341 and 3524-5798, with a multiple cloning region between nucleotides 341 and 3524 of Ad5, included the following three manipulations carried out in sequential cloning steps as follows:

(1) The left ITR region was extended to include the *Pac1* site at the junction between the vector backbone and the adenovirus left ITR sequences. This allow for easier manipulations using the bacterial homologous recombination system.

(2) The packaging region was extended to include sequences of the wild-type (WT) adenovirus from 342 bp to 450 bp inclusive.

(3) The area downstream of pIX was extended 13 nucleotides (i.e., nucleotides 3511-3523 inclusive).

These modifications (Figure 4) effectively reduced the size of the E1 deletion without overlapping with any part of the E1A/E1B gene present in the transformed PER.C6[®] cell line. All manipulations were performed by modifying the Ad shuttle vector pdelE1sp1A.

Once the modifications were made to the shuttle vector, the changes were incorporated into the original Ad5 adenovector backbones (pAdHVO and pAdHVE3) by bacterial homologous recombination using *E. coli* BJ5183 chemically competent cells.

EXAMPLE 5

Construction of Modified Adenovector Backbones (E3+ and E3-)

The original adenovectors pAdHVO (comprising all Ad5 sequences except those nucleotides encompassing the E1 and E3 regions) and pAdHVE3 (comprising all Ad5 sequences except those nucleotides encompassing the E1 region), were each reconstructed so that they contained the modifications to the E1 region. This was accomplished by digesting the newly modified shuttle vector (MRKpdeIE1 shuttle) with *Pac*I and *Bst*Z1101 and isolating the 2,734 bp fragment which corresponds to the adenovirus sequence. This fragment was co-transformed with DNA from either *Cla*I linearized pAdHVO (E3- adenovector) or *Cla*I linearized pAdHVE3 (E3+adenovector) into *E. coli* BJ5183 competent cells. At least two colonies from each transformation were selected and grown in Terrific™ broth for 6-8 hours until turbidity was reached. DNA was extracted from each cell pellet and then transformed into *E. coli* XL1 competent cells. One colony from each transformation was selected and grown for plasmid DNA purification. The plasmid was analyzed by restriction digestions to identify correct clones. The modified adenovectors were designated MRKpAdHVO (E3- plasmid) and MRKpAdHVE3 (E3+ plasmid). Virus from these new adenovectors (MRKHVO and MRKHVE3, respectively) as well as the old version of the adenovectors were generated in the PER.C6® cell lines to accommodate the following series of viral competition experiments. In addition, the multiple cloning site of the original shuttle vector contained *Cla*I, *Bam*HI, *Xho*I, *Eco*RV, *Hind*III, *Sal*I, and *Bgl*II sites. This MCS was replaced with a new MCS containing *Not*I, *Cla*I, *Eco*RV and *Asc*I sites. This new MCS has been transferred to the MRKpAdHVO and MRKpAdHVE3 pre-plasmids along with the modification made to the packaging region and pIX gene.

EXAMPLE 6

Analysis of the Effect of the Packaging Signal Extension

To study the effects of the modifications made to the E1 deletion region, the viruses obtained from the original backbone (pAdHVE3) and the new backbone (MRKpAdHVE3) were mixed together in equal MOI ratios (1:1 and 5:5) and passaged through several rounds; see Figure 5, Expt.#1. Both of the viruses in the experiment contained the E3 gene intact and did not contain a transgene. The only difference between the two viruses was within the region of the E1 deletion. Following the coinfection of the viruses at P1 (passage 1), the mixtures were propagated through an additional 4 passages at which time the cells were harvested

and the virus extracted and purified by CsCl banding. The viral DNA was extracted and digested with *HindIII* and the digestion products were then radioactively labeled. For the controls, the respective pre-plasmids (pAdHVE3 ("OLD E3+"); MRKpAdHVE3 ("NEW E3+")) were also digested with *HindIII* (and *Pac1* to remove the vector backbone) and subsequently labeled with [³³P]dATP. The radioactively labeled digestion products were subjected to gel electrophoresis and the gel was dried down onto Whatman paper before being exposed to autoradiographic film. Figure 6 clearly shows that the new adenovirus which has the addition made to the packaging signal region has a growth advantage compared with the original adenovirus. In the experiments performed (at either ratio tested), only the digestion bands pertaining to the newly modified virus were present. The diagnostic band of size 3,206 (from the new virus) was clearly present. However, there was no evidence of the diagnostic band of size 2,737 bp expected from the original virus.

EXAMPLE 7

Analysis of the Effect of the E3 Gene

The second set of the virus competition study involved mixing equal MOI ratio (1:1) of the newly modified viruses, that obtained from MRKpAdHVO and MRKpAdHVE3 (Figure 5, Expt. #2). In this set, both viruses had the new modifications made to the E1 deletion. The first virus (that from MRKpAdHVO) does not contain an E3 gene. The second virus (that from MRKpAdHVE3) does contain the E3 gene. Neither of the viruses contain a transgene. Following co-infection of the viruses, the mixtures were propagated through an additional 4 passages at which time the cells were harvested and the total virus extracted and purified by CsCl banding. The viral DNA was extracted and digested with *HindIII* and the digestion products were then radioactively labeled. For the controls, the respective pre-plasmids MRKpAdHVO ("NEW E3-"); MRKpAdHVE3 ("NEW E3+") were also digested with *HindIII* (and *Pac1* to remove the vector backbone) and then labeled with [³³P]dATP. The radioactively labeled digestion products were subjected to gel electrophoresis and the gel was dried down onto Whatman paper before being exposed to autoradiographic film. Figure 6 shows the results of the viral DNA analysis of the E3+ virus and E3- virus mixing experiment. The diagnostic band corresponding to the E3+ virus (5,665 bp) was present in greater amount compared with the diagnostic band of 3,010 bp corresponding to the E3- virus. This indicates that the virus that contains the E3 gene is able to amplify more rapidly

compared with the virus that does not contain an E3 gene. This increased amplification capacity has been confirmed by growth studies; see Table 4 below.

EXAMPLE 8

5 Construction of the new shuttle vector containing modified gag transgene –
“MRKpdelE1-CMV(no intron)-FLgag-bGHpA”

The modified plasmid pV1JnsCMV(no intron)-FLgag-bGHPA was digested with *MscI* overnight and then digested with *SfiI* for 2 hours at 50°C. The DNA was then treated with Mungbean nuclease for 30 mins at 30°C. The DNA mixture was desalted using the Qiaex II kit and then Klenow treated for 30 mins at 37°C to fully blunt the ends of the transgene fragment. The 2,559 bp transgene fragment was then gel purified. The modified shuttle vector (MRKpdeI1 shuttle) was linearized by digestion with *EcoRV*, treated with calf intestinal phosphatase and the resulting 6,479 bp fragment was then gel purified. The two purified fragments were then ligated together and several dozen clones were screened to check for insertion of the transgene within the shuttle vector. Diagnostic restriction digestion was performed to identify those clones carrying the transgene in the E1 parallel and E1 anti-parallel orientation. This strategy was followed to clone in the other gag transgenes in the MRKpdeI1 shuttle vector.

EXAMPLE 9

Construction of the MRK FG Adenovectors

The shuttle vector containing the HIV-1 gag transgene in the E1 parallel orientation, MRKpdeIE1-CMV(no intron)-FLgag-bGHPA, was digested with *Pac*I. The reaction mixture was digested with *Bsf*Z171. The 5,291 bp fragment was purified by gel extraction. The MRKpAdHVE3 plasmid was digested with *Cl*aI overnight at 37°C and gel purified. About 100 ng of the 5,290 bp shuttle +transgene fragment and ~100 ng of linearized MRKpAdHVE3 DNA were co-transformed into *E. coli* BJ5183 chemically competent cells. Several clones were selected and grown in 2 ml Terrific™ broth for 6-8 hours, until turbidity was reached. The total DNA from the cell pellet was purified using Qiagen alkaline lysis and phenol chloroform method. The DNA was precipitated with isopropanol and resuspended in 20 µl dH₂O. A 2 µl aliquot of this DNA was transformed into *E. coli* XL-1 competent cells. A single colony from each separate transformation was selected and grown overnight in 3 ml LB +100 µg/ml ampicillin. The DNA was isolated using Qiagen columns. A positive clone was identified by digestion with the restriction enzyme *Bsf*EII which cleaves

within the gag gene as well as the plasmid backbone. The pre-plasmid clone is designated MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA and is 37,498 bp in size. This strategy was followed to generate E3- and E3+ versions of each of the other gag transgene constructions in both E1 parallel and E1 anti-parallel versions. Figures 7A, 7B and 7C show the various combinations of adenovectors constructed.

EXAMPLE 10

Plasmid Competition Studies

A series of plasmid competition studies was carried out. Briefly, the screening of the various combinations of new constructs was performed by mixing equal amounts of each of two competing plasmids. In the experiment shown in Figure 8A, plasmids containing the same transgene but in different orientations were mixed together to create a "competition" between the two plasmids. The aim was to look at the effects of transgene orientation. In the experiment shown in Figure 8B, plasmids containing different polyadenylation signals (but in the same orientation) were mixed together in equal amounts. The aim was to assess effects of polyA signals. Following the initial transfection, the virus was passaged through ten rounds and the viral DNA analyzed by radioactive restriction analysis.

Analysis of the viral species from the plasmid mixing experiment (Figure 8A) showed that adenovectors which had the transgene inserted in the E1 parallel orientation amplified better and were able to out-compete the adenovirus which had the transgene inserted in the E1 anti-parallel orientation. Viral DNA analysis of the mixtures at passage 3 and certainly at passage 6, showed a greater ratio of the virus carrying the transgene in the E1 parallel orientation compared with the E1 antiparallel version. By passage 10, the only viral species observed was the adenovector with the transgene in the E1 parallel orientation for both transgenes tested (hCMV(no intron)-FLgag-bGHpA and hCMV(no intron)-FLgag-SPA).

Analysis of the viral species from the plasmid mixing experiment #2 (Figure 8B) at passages 3 and 6 showed that the polyadenylation signals tested (bGHpA and SPA) did not have an effect on the growth of the virus. Even at passage 10 the two viral species in the mixture were still present in equal amounts.

EXAMPLE 11

Virus generation of an enhanced adenoviral construct – “MRK Ad5 HIV-1gag”

The results obtained from the competition study allowed us to make the following conclusions: (1) The packaging signal extension is beneficial; (2) Presence of E3 does enhance viral growth; (3) E1 parallel orientation is recommended; and (4) PolyA signals have no effect on the growth of the adenovirus.

MRK Ad5 HIV-1 gag exhibited the most desirable results. This construct contains the hCMV(no intron)-FLgag-bGHpA transgene inserted into the new E3+ adenovector backbone, MRKpAdHVE3, in the E1 parallel orientation. We have designated this adenovector MRK Ad5 HIV-1 gag. This construct was prepared as outlined below:

The pre-plasmid MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA was digested with *PacI* to release the vector backbone and 3.3 µg was transfected by calcium phosphate method (Amersham Pharmacia Biotech.) in a 6 cm dish containing PER.C6[®] cells at ~60% confluence. Once CPE was reached (7-10 days), the culture was freeze/thawed three times and the cell debris pelleted. 1 ml of this cell lysate was used to infect into a 6 cm dish containing PER.C6[®] cells at 80-90% confluence. Once CPE was reached, the culture was freeze/thawed three times and the cell debris pelleted. The cell lysate was then used to infect a 15 cm dish containing PER.C6[®] cells at 80-90% confluence. This infection procedure was continued and expanded at passage 6. The virus was then extracted from the cell pellet by CsCl method. Two bandings were performed (3-gradient CsCl followed by a continuous CsCl gradient). Following the second banding, the virus was dialyzed in A105 buffer. Viral DNA was extracted using pronase treatment followed by phenol chloroform. The viral DNA was then digested with *HindIII* and radioactively labeled with [³³P]dATP. Following gel electrophoresis to separate the digestion products the gel was dried down on Whatman paper and then subjected to autoradiography. The digestion products were compared with the digestion products from the pre-plasmid (that had been digested with *PacI/HindIII* prior to labeling). The expected sizes were observed, indicating that the virus had been successfully rescued. This strategy was used to rescue virus from each of the various adenovector plasmid constructs prepared.

EXAMPLE 12

Stability Analyses

To determine whether the various adenovector constructs (e.g., MRK Ad5 HIV-1 gag) show genetic stability, the viruses were each passaged continually. The viral DNA was analyzed at passages 3, 6 and 10. Each virus maintained its correct genetic structure. In addition, the stability of the MRK Ad5 HIV-1 gag was analyzed under propagation conditions similar to that performed in large scale production. For this analysis, the transfections of MRK Ad5 HIV-1 gag as well as three other adenoviral vectors were repeated and the virus was purified at P3. The three other adenovectors were as follows: (1) that comprising hCMV(no intron)-Flgag with a bGHpA terminator in an E3- adenovector backbone; (2) that comprising hCMV(no intron)-Flgag with a SPA termination signal in an E3+ adenovector backbone, and that comprising a mCMV-Flgag with a bGHpA terminator in an E3+ adenovector backbone. All of the vectors have the transgene inserted in the E1 parallel orientation. Viral DNA was analyzed by radioactive restriction analysis to confirm that it was correct before being delivered to fermentation cell culture for continued passaging in serum-free media. At P5 each of the four viruses were purified and the viral DNA extracted for analysis by the restriction digestion and radiolabeling procedure. This virus has subsequently been used in a series of studies (*in vitro* gag expression in COS cells, rodent study and rhesus monkey study) as will be described below. The viruses from P5 are shown in Figure 9.

The passaging under serum-free conditions was continued for the MRKHVE3 (transgene-less, obtained from MRKpAdHVE3 pre-plasmid) and the MRKAd5HIV-1gag (obtained from MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA pre-plasmid) viruses. Figure 10 shows viral DNA analysis by radioactive restriction digestion at passage 11 for MRKHVE3, MRKAd5HIV-1gagE3-, and passage 11 and 12 for MRKAd5HIV-1gag. Aside from the first lane which is the DNA marker lane, the next three lanes are virus from the pre-plasmid controls (controls based on the original virus) - MRKpAdHVE3 (also referred to as "pMRKHVE3"), MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA, and pMRKAd5gag(E3-), respectively. As seen in Figure 10, each of the viral DNA samples show the expected bands with no extraneous bands showing. This signifies that there are no major variant adenovirus species present that can be detected by autoradiography.

Figure 11 shows the results of viral competition study between MRKHVE3 and MRKAd5HIV-1gag. These viruses were mixed together at equal MOI (140 viral

particles each; 280 vp total) at passage 6 and continued to be passaged until P11.

Aside from the first lane which is the DNA marker lane, the next two lanes are the pre-plasmid controls obtained from MRKpAdHVE3 and MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA. The next two lanes are the viral DNA from the starting viral material at passage six. The last two lanes are the competition studies performed in duplicate. The data in Figure 11 shows the effect the gag transgene in culture.

5 Growth of a MRKAd5gag virus was compared with growth of a "transgene-less" MRKHVE3. These two viruses were infected at the same MOI (i.e. 140 vp each) at passage 6 and then passaged through to passage 11 and the viral pool was analyzed by radioactive restriction analysis. The data shows that one virus did not out compete the other. Therefore, the gag transgene did not show obvious signs of toxicity to the adenovirus.

Analysis by *HindIII* digestion shows that each virus specie is present in approximately equal amounts. As above, there does not appear to be signs of any extraneous bands. Figure 12 shows higher passage numbers for MRKAd5HIV-1gag grown under serum-containing conditions. The genome integrity again has been maintained and there is no evidence of rearrangements, even at the highest passage level (P21).

Each of the four vectors shown in Figure 9 were analyzed for amplification capacity. Table 4 below shows the QPA analysis used in the estimation of viral amplification ratios at P4. The determination of the amplification ratio for the original HIV-1 gag construct is based on the clinical lot at P12. It has been shown that amplification rates increases with higher passage number for the original virus. The reason for this observation is due to the emergence of variants which exhibit increased growth rates compared to the intact adenovector. With continued passaging of the original Ad gag vector, the level of variants increases and hence amplification rates increase also.

25 The MRK Ad5 HIV-1 gag virus has also been continually passaged under process conditions (i.e., serum-free media). Viral DNA extracted from passages 11 and 12 show no evidence of rearrangement.

Table 4:
Amplification Ratios Based on AEX and QPA Analysis of
Virus Amplification from Passage 3 to Passage 4.

Ad gag construct	Amplification Ratio
MRKAd5gag	470
HCMV-Flgag-bGHpA [E3-]	115
HCMV-Flgag-SPA [E3+]	320
mCMV-FLgag-bGHpA [E3+]	420
Original construct *	40 - 50

* This estimation is based on the clinical lot growth characteristics at Passage 12.

EXAMPLE 13

Analytical Evaluation of the enhanced Ad5 Constructs

To study the effects of the transgene and the E3 gene on virus amplification, the enhanced adenoviral vector, MRK Ad5 HIV-1 gag, along with its transgene-less version (MRKpAdHVE3) and its E3- version (MRK Ad5 HIV-1 gag E3-), was studied for several passages under serum-free conditions. Table 5A shows the amplification ratios determined for passages P3 to P8 for MRK Ad5 HIV-1 gag. Within a certain MOI range, it has been determined that the virus output is directly proportional to the virus input. Therefore, the greater the number of virus particles per cell at infection, the greater the virus amount produced. Viral amplification ratios, on the other hand, are inversely proportional to the virus input. The lower the virus input, the greater the amplification ratio.

Table 5B shows the amplification rates of the new E3+ vector backbone MRKpAdHVE3. It has a significantly lower rate of amplification compared with the gag transgene containing version. This may be contributed to the larger size MRK Ad5 HIV-1 gag since it contains the transgene. This inclusion of the transgene brings the size of the adenovirus closer to the size of a wild type Ad5 virus. It is well known that adenoviruses amplify best when they are at close to their wild type genomic size.

Wild type Ad5 is 35,935 bp. The MRKpAdHVE3 is 32,905 bp in length. The enhanced adenovector MRK Ad5 HIV-1 gag is 35,453bp (See Figure 14 for vector map; see also Figure 15A-X show the complete pre-adenoviral vector sequence, which includes an additional 2,021 bp of the vector backbone).

- 5 Table 5C shows the amplification rates of the new E3- gag containing virus MRK Ad5 HIV-1 gag E3-. Once again, this virus shows lower growth rate than the enhanced adenoviral vector. This may be attributed to the decreased sized of this virus (due to the E3 gene deletion) compared with wild type Ad5. The MRK Ad5 HIV-1 gag E3- virus is 32,810 bp in length. This can be compared with the wild type
- 10 Ad5 which is 35,935 bp and MRK Ad5 HIV-1 gag which is 35,453 bp in length.

Table 5A: Amplification ratios determined by AEX and QPA for **MRKAd5gag** over several continuous passaging in serum free media. Following P5, two replicate samples were taken (rep-1 and rep-2) and analyzed.

MRKAd5gag rep1

	Xv (10 ⁶ cells/ml), Viability (%) Infection Harvest	Harvest Time h.p.i.	Cell Passage Number	Titer 10 ¹⁰ vp/ml culture	Titer 10 ⁶ vp/cell	QPA 10 ⁸ TCID ₅₀ /ml	Ratio AEX:QPA	Amplification Ratio	AEX Internal Control
P4	1.49, 81%	0.68, 50%	44	46	8.7	8.9	1.72	50	470 (MOI = 125)
P5	1.38, 93%	0.66, 47%	48	49	8.7	4.9	1.38	49	170
P6	1.04, 94%	0.68, 77%	47	48	5.8	5.6	1.42	41	200
P7	1.50, 84%	0.96, 61%	49.5	50	3.9	1.4	0.97	40	50
P7	1.09, 97%	0.76, 69%	50	52	5.2	4.7	1.70	31	170
P8	1.03, 94%	0.68, 64%	47.5	54	9.0	8.7	1.10	62	310
P9	0.89, 95%	0.99, 73%	47.5	56	4.4	4.9	1.03	43	175
P10	1.09, 91%	1.08, 66%	47.5	58	3.0	2.8	1.16	28	100
P11	1.19, 88%	0.98, 65%	47	60	3.6	3.0	1.15	31	110
P12	0.98, 91%	0.85, 63%	47.5	47	5.4	5.5	1.20	45	200
P13	1.00, 88%	0.70, 67%	49	49	5.8	5.8	1.11	62	210
P14	1.94, 92%	0.88, 67%	46	53	6.6	4.4			160
P15	0.97, 95%	0.64, 66%	47	47	6.9	7.1			250
									3.12 2.84 2.70 2.60 2.70 2.66 2.60 3.18 3.18 3.28 3.27 3.12 2.91

Table 5B: Amplification ratios determined by AEX and QPA for **MRKHVE3** over several continuous passaging in serum free media. **MRKHVE3** is the new vector backbone which does NOT carry a transgene.

MRKHVE3

	Xv (10 ⁶ cells/ml), Viability (%) Infection Harvest	Harvest Time h.p.i.	Cell Passage Number	Titer 10 ¹⁰ vp/ml culture	Titer 10 ⁶ vp/cell	QPA 10 ⁸ TCID ₅₀ /ml	Ratio AEX:QPA	Amplification Ratio	AEX Internal Control
P4	1.10, 97%	1.28, 78%	49	54	4.1	3.8	1.70	25	300 (MOI = 125)
P5	0.92, 89%	1.18, 77%	47	48	4.3	4.7	1.24	35	170
P6	1.55, 88%	1.26, 76%	49.5	50	1.2	0.8	0.56	21	30
P6	1.09, 97%	1.11, 81%	49	52	4.0	3.6	1.16	34	130
P7	1.17, 91%	1.22, 91%	47.5	54	3.7	3.2	0.50	74	110
P8	0.98, 88%	1.41, 63%	48	56	2.1	2.1	0.47	45	75
P9	1.20, 89%	1.26, 81%	47.5	58	0.8	0.7	0.29	28	25
P10	0.99, 82%	1.55, 86%	47	60	2.3	2.3	0.43	53	80
P11	1.07, 96%	1.25, 83%	48	47	2.7	2.5	0.41	66	90
P12	0.80, 91%	1.14, 80%	49.5	49	5.9	7.4	0.48	123	260
P13	1.96, 95%	1.14, 85%	45.5	53	5.8	3.0			110
P14	0.97, 95%	1.03, 98%	48.5	47	9.4	9.7			350
P15	0.87, 99%	0.97, 69%	49.5	49	5.3	6.1			218
									3.12 2.84 2.70 2.60 2.70 2.66 2.60 3.18 3.18 3.28 3.27 3.12 2.91 2.78 2.52

Table 5C. Amplification ratios determined by AEX and QPA for MRKAd5gag(E3-) over several continuous passaging in serum free media. This construct is identical to the MRKAd5gag construct except that this version is DELETED of the E3 gene.

5

MRKAd5gag(E3-)

	Xv (10 ⁶ cells/ml), Infection	Viability (%), Harvest	Harvest Time h.p.i.	Cell Passage Number	Titer 10 ⁶ vp/ml culture	Titer 10 ⁶ vp/cell	QPA 10 ⁶ TCID ₅₀ /ml	Ratio AEX:QPA	Amplification Ratio	AEX Internal Control
P4	1.62, 77%	1.12, 62%	47.5	46	2.0	1.2	0.92	20	100 (MOI=125)	
P5	1.16, 92%	0.62, 43%	49	49	3.3	2.9	0.99	34	100	
P6	1.71, 86%	0.20, 10%	49	50	4.7	2.7	1.70	28	100	
P6	1.09, 97%	0.63, 54%	49.5	52	5.4	5.0	1.76	31	180	
P7	1.17, 91%	0.98, 72%	47.50	54	7.1	6.1	0.67	106	220	
P8	0.98, 88%	0.77, 48%	48	56	3.1	3.2	0.66	47	115	3.12
P9	1.20, 89%	1.03, 72%	48	58	1.8	1.5	0.57	32	55	2.84
P10	0.99, 82%	0.80, 62%	46.5	60	3.2	3.2	0.68	47	115	2.70
P11	1.07, 96%	0.98, 70%	48.5	47	5.9	5.5	0.68	87	200	2.60
P12	0.80, 91%	0.67, 59%	50	49	5.1	6.4	0.72	71	230	2.86
P13	1.86, 95%	0.91, 59%	45.5	53	7.4	3.8			135	3.18
P14	0.97, 96%	0.81, 74%	48	47	6.8	7.0			250	3.28
P15	0.87, 99%	0.84, 66%	49	49	4.8	5.5			196	3.27
										3.12
										2.91
										2.78
										2.52

EXAMPLE 14

Gag Expression Analysis of the Novel Constructs

In vitro gag analysis of the MRK Ad5 HIV-1 gag and the original HIV-gag vectors (research and clinical lot) show comparable gag expression. The clinical lot shows only a slightly reduced gag expression level. The most noticeable difference is with the mCMV vector. This vector shows roughly 3 fold lower expression levels compared with the other vectors tested (which all contain hCMV promoters). The mCMV-FLgag with bGHpA assay was performed three times using different propagation and purification lots and it consistently exhibited weaker gag expression.

EXAMPLE 15

Evaluation of MRK Ad5 HIV-1 gag and Other gag-Containing Adenovectors in Balb/c Mice

Cohorts of 10 balb/c mice were vaccinated intramuscularly with escalating doses of MRK Ad5 HIV-1 gag, and the research and clinical lots of original Ad5HIV-1gag. Serum samples were collected 3 weeks post dose 1 and analyzed by anti-p24 sandwich ELISA.

Anti-p24 titers in mice that received MRK Ad5 HIV-1 gag (10^7 and 10^9 vp(viral particle) doses) were comparable (Figure 13) to those of the research lot of Ad5HIV-1 gag, for which much of the early rhesus data were generated on. These titers were also comparable when E3 is deleted (MRKAd5hCMVgagbGHpA(E3-)) or SPA is substituted for bGHpA terminator (MRKAd5 hCMV-gag-SPA (E3+)) or murine CMV promoter is used in place of hCMV (MRKAd5 mCMV-gag-bGHpA (E3+)) in the MRKAd5 backbone.

The results shown in Table 7 indicate that the three other vectors (in addition to the preferred vector, MRK Ad5 HIV-1 gag, are also capable of inducing strong anti-gag antibody responses in mice. Interestingly enough, while the mCMV-FLgag construct containing bGHpA and E3+ in an E1 parallel orientation showed lowest gag expression in the COS cell *in vitro* infection (Table 6) in comparison with the other vectors tested, it generated the greatest anti-gag antibody response this *in vivo* Balb/c study. Table 7 also shows a dose response in anti-gag antibody production in both the research and the clinical lot. As expected, the clinical lot shows reduced anti-gag antibody induction at each dosage level compared to the same dosage used for the research lot.

Table 6: *In vitro* analysis for gag expression in COS cells by Elisa assay.

Viral Vectors ^a	$\mu\text{g gag}/4.8 \times 10^5 \text{ COS}/10^8 \text{ parts}/48\text{hr}$
MRKAd5gag ^b	1.40
Clinical lot Ad5gag ^c	1.28
Research lot Ad5gag ^d	1.32
MCMVFL-gagbGHpA ^e	0.42

^a $A_{260\text{nm}}$ absorbance readings taken for viral particle determinations.

^b MRKAd5gag was produced in serum free conditions and purified at P5.

^c Clinical lot# Ad5gagFN0001

^d Research Ad5FLgag lot# 6399

^e mCMVFL-gagbGHpA was produced in serum free conditions and purified at P5.

Table 7: mHIV020 Anti-p24 Ab Titers in Balb/c mice (n=10) vaccinated with various Adgag constructs and lots (3 week post dose1).

Group ID	Vaccine	Dose (vp)	GMT	SE upper	SE lower
1	^a MRKAd5gag	10 ⁷	25600	5877	4780
2	"	10 ⁹	409600	94028	76473
3	hCMV FL-gag bGHpA [E3-] →	10 ⁷	7352	2077	1620
4	"	10 ⁹	235253	59767	47659
5	hCMV FL-gag SPA [E3+] →	10 ⁷	12800	9905	236
6	"	10 ⁹	310419	99181	75165
7	^b mCMV FL-gag bGHpA [E3+] →	10 ⁷	44572	23504	15389
8	"	10 ⁹	941014	239068	190636
9	^c hCMV FL-gag bGHpA [E3-] ←	10 ⁷	3676	934	745
10	"	10 ⁹	117627	17491	15227
11	research lot hCMV IntronA FL-gag bGHpA [E3-] <-	10 ⁶	528	262	175
12	"	10 ⁷	14703	5274	3882
13	"	10 ⁸	58813	14942	11915
14	"	10 ⁹	204800	53232	42250
15	clinical lot hCMVintronA FL-gag bGHpA [E3-] <-	10 ⁶	230	82	61
16	"	10 ⁷	4222	3405	1138
17	"	10 ⁸	19401	3939	3274
18	"	10 ⁹	89144	25187	19639
19	Naïve	none	93	7	6

*2x50 µL i.m. (quad) injections/animal

P.I.s: Youll, Chen, Casimiro

Vaccination: T. Toner, Q. Su

Assay: M. Chen

^aThe structure of MRKAd5gag is: hCMVFL-gagbGHpA [E3+] → The same lot of MRKAd5gag used in this rodent study was used in the Rhesus monkey study (Tables 7 and 8).

^bThe same lot of mCMVFL-gagbGHpA[E3+] used in the *in vitro* study (Table 6) was used here.

^cThis construct was designed by Volker Sandig. It contains a shorter version of the hCMV promoter than that used in the MRK constructs. The adenovector backbone is identical to the original backbone used in the original Adgag vector. Expression at 10⁶ dose from this vector is 7 fold lower than the same dose of the MRKAd5gag and 4 fold lower than the research lot.

EXAMPLE 16

Comparison of Humoral and Cellular Responses Towards the Original Ad-gag Construct with the New MRK Ad5 HIV-1 gag in Rhesus Monkeys

- 5 Cohorts of 3 rhesus monkeys were vaccinated intramuscularly with MRK Ad5 HIV-1 gag or the clinical Ad5gag bulk at two doses, 10¹¹ vp and 10⁹ vp. Immunizations were conducted at week 0, 4, and 25. Serum and PBMC samples were collected at selected time points. The serum sample were assayed for anti-p24 Ab titers (using competitive based assay) and the PBMCs for antigen-specific IFN-
 10 gamma secretion following overnight stimulation with gag 20-mer peptide pool (via ELISpot assay).

The results shown in Table 8 indicate comparable responses with respect to the generation of anti-gag antibodies. The frequencies of gag-specific T cells in

- peripheral blood as summarized in Table 9 demonstrate a strong cellular immune response generated after a single dose with the new construct MRK Ad5 HIV-1 gag. The responses are also boostable with second dose of the same vector. The vector is also able to induce CD8+ T cell responses (as evident by remaining spot counts after
- 5 CD4+ depletion of PBMCs) which are responsible for cytotoxic activity.

Table 8 Anti-p24 antibody titers (in mMU/mL) in rhesus macaques immunized with gag-expressing adenovectors (Protocol HIV203).

Vaccine	Pre	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 25	Wk 28
MRKAd5gag^a, 10¹¹ vp								
97N010	<10	118	5528	11523	7062	21997	ND	51593
97N116	<10	62	772	1447	1562	2174	ND	20029
98X007	<10	66	3353	6156	6845	3719	ND	24031
MRKAd5gag, 10⁹ vp								
97N120	<10	51	204	318	366	482	ND	6550
97N144	<10	18	118	274	706	888	ND	7136
98X008	<10	15	444	386	996	1072	ND	12851
Ad5gag^b, Clinical Lot, 10¹¹ vp								
97X001	<10	87	2579	4718	7174	7250	ND	69226
97N146	<10	72	3604	7380	7526	18906	ND	60283
98X009	<10	78	4183	3946	3124	6956	ND	26226
Ad5gag, Clinical Lot, 10⁹ vp								
97N020	<10	<10	143	371	390	1821	ND	17177
97X003	<10	<10	39	93	156	596	ND	2053
98X012	<10	81	342	717	956	1558	ND	11861
^a MRKAd5gag (hCMV, bGHpA, E3+)								
^b original Ad5gag vector (hCMV/intron A, bGHpA, E3-), lot#FN0001								
ND, not determined								

Table 9. Number of gag-specific T cells per million peripheral blood mononuclear cells (PBMCs) in rhesus monkeys immunized with gag-expressing adenovectors. Also included are those frequencies in PBMCs depleted of CD4⁺ T cells.

Grp #	Vaccination T=0,4,25 wks	Monkey ID	T=4 Wk		T=6 Wk		T=11 Wk		T=16 Wk		T=25 Wk		T=28 Wk	
			Media ^a	Gag H ^b	Media	Gag H	Media	Gag H	Media	Gag H	Media	Gag H	Media	Gag H
1	MRKAd5gag 10 ¹¹ vp	97N010	6	89	0	395	0	1058	0	1174	3	775	4	1074
		97N010(CD4-)	4	38			3	993			0	76	0	594
		97N116	1	398	1	609	0	534	4	395	1	261	0	408
		97N116(CD4-)	11	676			0	593			0	184	0	666
		98X007	10	579	0	1304	3	2193	1	2118	3	1588	0	2113
		98X007(CD4-)	20	965			0	2675			0	1656	0	1278
2	MRKAd5gag 10 ⁹ vp	97N120	5	275	1	249	4	141	4	119	9	206	4	219
		97N120(CD4-)	11	170			0	85			0	75	1	219
		97N144	3	236	6	438	1	318	3	256	1	98	5	373
		97N144(CD4-)	6	148			0	285			ND	ND	0	625
		98X008	4	368	1	1090	3	891	4	673	3	473	5	735
		98X008(CD4-)	14	696			0	1175			0	391	4	848
3	Ad5gag clinical lot 10 ¹¹ vp	97X001	0	261	1	485	0	817	0	1220b	1	894	0	1858
		97X001(CD4-)	10	283			3	996			0	1010	0	1123
		97N146	3	150	1	465	0	339	1	1272	3	1238	3	1785
		97N146(CD4-)	6	133			0	370			0	654	0	971
		98X009	0	93	3	339	3	559	0	896	1	384	0	1748
		98X009(CD4-)	0	73			0	333			0	225	0	644
4	Ad5gag clinical lot 10 ⁹ vp	97N020	3	30	1	101	0	66	0	36	0	26	0	41
		97N020(CD4-)	10	29			0	15			0	1	0	16
		97X003	4	68	5	134	0	18	1	38	4	38	6	81
		97X003(CD4-)	9	40			0	6			0	4	0	19
		98X012	5	95	3	54	1	34	0	18	0	20	1	121
		98X012(CD4-)	11	70			0	11			0	8	0	41
5	Naïve	96R041	6	8	1	1	0	0	0	0	0	0	1	0
		053F	14	18	5	16	20	14	0	15	0	15	24	9

Based on either 4x10⁶ or 2x10⁶ cells per well (depending on spot density)

ND, not determined

^aMock or no peptide control

^bPool of 20-aa peptides overlapping by 10 aa and encompassing the gag sequence

5

The adenovectors described herein and, particularly, MRK Ad5 HIV-1 gag, represent very promising HIV-gag adenovectors with respect to their enhanced growth characteristics in both serum and, more importantly, in serum-free media conditions. In comparison with the current HIV-1 gag adenovector construct, MRK Ad5 HIV-1 gag shows a 5-10 fold increased amplification rate. We have shown that it is genetically stable at passage 21. This construct is able to generate significant cellular immune responses *in vivo* even at a relatively low dose of 10⁹ vp. The potency of the MRKAd5gag construct is comparable to, if not better than the original HIV-1gag vector as shown in this rhesus monkey study.

15

EXAMPLE 17

CODON OPTIMIZED HIV-1 POL AND CODON OPTIMIZED HIV-1 POL MODIFICATIONS

20

The open reading frames for the various synthetic *pol* genes disclosed herein comprise coding sequences for the reverse transcriptase (or RT which consists of a polymerase and RNase H activity) and integrase (IN). The protein sequence is based

on that of Hxb2r, a clonal isolate of IIB; this sequence has been shown to be closest to the consensus clade B sequence with only 16 nonidentical residues out of 848 (Korber, et al., 1998, Human retroviruses and AIDS, Los Alamos National Laboratory, Los Alamos, New Mexico). The skilled artisan will understand after

5 review of this specification that any available HIV-1 or HIV-2 strain provides a potential template for the generation of HIV pol DNA vaccine constructs disclosed herein. It is further noted that the protease gene is excluded from the DNA vaccine constructs of the present invention to insure safety from any residual protease activity in spite of mutational inactivation. The design of the gene sequences for both wild-

10 type (wt-pol) and inactivated pol (IA-pol) incorporates the use of human preferred ("humanized") codons for each amino acid residue in the sequence in order to maximize *in vivo* mammalian expression (Lathe, 1985, *J. Mol. Biol.* 183:1-12). As can be discerned by inspecting the codon usage in SEQ ID NOs: 1, 3, 5 and 7, the following codon usage for mammalian optimization is preferred: Met (ATG), Gly

15 (GGC), Lys (AAG), Trp (TGG), Ser (TCC), Arg (AGG), Val (GTG), Pro (CCC), Thr (ACC), Glu (GAG); Leu (CTG), His (CAC), Ile (ATC), Asn (AAC), Cys (TGC), Ala (GCC), Gln (CAG), Phe (TTC) and Tyr (TAC). For an additional discussion relating to mammalian (human) codon optimization, see WO 97/31115 (PCT/US97/02294), which, as noted elsewhere in this specification, is hereby incorporated by reference. It

20 is intended that the skilled artisan may use alternative versions of codon optimization or may omit this step when generating HIV pol vaccine constructs within the scope of the present invention. Therefore, the present invention also relates to non-codon optimized versions of DNA molecules and associated recombinant adenoviral HIV vaccines which encode the various wild type and modified forms of the HIV Pol

25 protein disclosed herein. However, codon optimization of these constructs is a preferred embodiment of this invention.

A particular embodiment of this portion of the invention comprises codon optimized nucleotide sequences which encode wt-pol DNA constructs (herein, "wt-pol" or "wt-pol (codon optimized)") wherein DNA sequences encoding the protease

30 (PR) activity are deleted, leaving codon optimized "wild type" sequences which encode RT (reverse transcriptase and RNase H activity) and IN integrase activity. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:1, the open reading frame being contained from an initiating Met residue at nucleotides 10-12 to a termination codon from nucleotides 2560-2562. SEQ ID NO:1 is as follows:

35 AGATCTACCA TGGCCCCCAT CTCCCCATT GAGACTGTGC CTGTGAAGCT GAAGCCTGGC
ATGGATGGCC CCAAGGTGAA GCAGTGGCCC CTGACTGAGG AGAAGATCAA GGCCCTGGTG

GAAATCTGCA CTGAGATGGA GAAGGAGGGC AAAATCTCCA AGATTGGCCC CGAGAACCCC
 TACAACACCC CTGTGTTTGC CATCAAGAAG AAGGACTCCA CCAAGTGGAG GAAGCTGGTG
 GACTTCAGGG AGCTGAACAA GAGGACCCAG GACTTCTGGG AGGTGCAGCT GGGCATCCCC
 CACCCCGCTG GCCTGAAGAA GAAGAAGTCT GTGACTGTGC TGGATGTGGG GGATGCCTAC
 5 TTCTCTGTGC CCCTGGATGA GGACTTCAGG AAGTACACTG CCTTCACCAT CCCCTCCATC
 AACAATGAGA CCCCTGGCAT CAGGTACCAG TACAATGTGC TGCCCCAGGG CTGGAAGGGC
 TCCCCTGCCA TCTTCCAGTC CTCCATGACC AAGATCCTGG AGCCCTTCAG GAAGCAGAAC
 CCTGACATTG TGATCTACCA GTACATGGAT GACCTGTATG TGGGCTCTGA CCTGGAGATT
 GGGCAGCACA GGACCAAGAT TGAGGAGCTG AGGCAGCACC TGCTGAGGTG GGGCTGACC
 10 ACCCCTGACA AGAAGCACCA GAAGGAGCCC CCCTTCCTGT GGATGGGCTA TGAGCTGCAC
 CCCGACAAGT GGACTGTGCA GCCCATTGTG CTGCCTGAGA AGGACTCCTG GACTGTGAAT
 GACATCCAGA AGCTGGTGGG CAAGCTGAAC TGGGCTCCC AAATCTACCC TGGCATCAAG
 GTGAGGCAGC TGTGCAAGCT GCTGAGGGG ACCAAGGCCC TGACTGAGGT GATCCCCCTG
 ACTGAGGAGG CTGAGCTGGA GCTGGCTGAG AACAGGGAGA TCCTGAAGGA GCCTGTGCAT
 15 GGGGTGTACT ATGACCCCTC CAAGGACCTG ATTGCTGAGA TCCAGAAGCA GGGCCAGGGC
 CAGTGGACCT ACCAAATCTA CCAGGAGCCC TTCAAGAACC TGAAGACTGG CAAGTATGCC
 AGGATGAGGG GGGCCACAC CAATGATGTG AAGCAGCTGA CTGAGGCTGT GCAGAAGATC
 ACCACTGAGT CCATTGTGAT CTGGGGCAAG ACCCCCAAGT TCAAGCTGCC CATCCAGAAG
 GAGACCTGGG AGACCTGGTG GACTGAGTAC TGGCAGGCCA CCTGGATCCC TGAGTGGGAG
 20 TTTGTGAACA CCCCCCCCCT GGTGAAGCTG TGGTACCAGC TGGAGAAGGA GCCCATTGTG
 GGGGCTGAGA CCTTCTATGT GGATGGGGCT GCCAACAGGG AGACCAAGCT GGGCAAGGCT
 GGCTATGTGA CCAACAGGGG CAGGCAGAAG GTGGTGACCC TGACTGACAC CACCAACCAG
 AAGACTGAGC TCCAGGCCAT CTACCTGGCC CTCCAGGACT CTGGCCTGGA GGTGAACATT
 GTGACTGACT CCCAGTATGC CCTGGGCATC ATCCAGGCCC AGCCTGATCA GTCTGAGTCT
 25 GAGCTGGTGA ACCAGATCAT TGAGCAGCTG ATCAAGAAGG AGAAGGTGTA CCTGGCCTGG
 GTGCCTGCCC ACAAGGGCAT TGGGGGCAAT GAGCAGGTGG ACAAGCTGGT GTCTGTGGC
 ATCAGGAAGG TGCTGTTTCT GGATGGCATT GACAAGGCCC AGGATGAGCA TGAGAAGTAC
 CACTCCAAC TGGAGGGCTAT GGCTCTGAC TTCAACCTGC CCCCTGTGGT GGCTAAGGAG
 ATTGTGGCCT CCTGTGACAA GTGCCAGCTG AAGGGGAGG CCATGCATGG GCAGGTGGAC
 30 TGCTCCCCCTG GCATCTGGCA GCTGGACTGC ACCACCTGG AGGGCAAGGT GATCCTGGTG
 GCTGTGCATG TGGCCTCCGG CTACATTGAG GCTGAGGTGA TCCCTGCTGA GACAGGCCAG
 GAGACTGCCT ACTTCCTGCT GAAGCTGGCT GGCAGGTGGC CTGTGAAGAC CATCCACACT
 GACAATGGCT CCAACTTCAC TGGGGCCACA GTGAGGGCTG CCTGCTGGTG GGCTGGCATC
 AAGCAGGAGT TTGGCATCCC CTACAACCCC CAGTCCCAGG GGGTGGTGA GTCCATGAAC
 35 AAGGAGCTGA AGAAGATCAT TGGGCAGGTG AGGGACCAGG CTGAGCACCT GAAGACAGCT
 GTGCAGATGG CTGTGTTTCT CCACAACCTT AAGAGGAAGG GGGGCATCGG GGGCTACTCC

GCTGGGGAGA GGATTGTGGA CATCATTGCC ACAGACATCC AGACCAAGGA GCTCCAGAAG
 CAGATCACCA AGATCCAGAA CTTCAAGGTG TACTACAGGG ACTCCAGGAA CCCCCTGTGG
 AAGGGCCCTG CCAAGCTGCT GTGGAAGGGG GAGGGGGCTG TGGTGATCCA GGACAACTCT
 GACATCAAGG TGGTGCCCAG GAGGAAGGCC AAGATCATCA GGGACTATGG CAAGCAGATG
 5 GCTGGGGATG ACTGTGTGGC CTCCAGGCAG GATGAGGACT AAAGCCCGGG CAGATCT (SEQ
 ID NO:1).

The open reading frame of the wild type pol construct disclosed as SEQ ID
 NO:1 contains 850 amino acids, disclosed herein as SEQ ID NO:2, as follows:

Met Ala Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro
 10 Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys
 Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys
 Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala
 Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg
 Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile
 15 Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Asp
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys
 Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile
 Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala
 Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln
 20 Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val Gly
 Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu Arg
 Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His Gln
 Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys
 Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
 25 Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile
 Tyr Pro Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr
 Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu
 Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr
 Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln
 30 Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys
 Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys
 Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile
 Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
 Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp
 35 Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu
 Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Asp Gly Ala Ala

Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly
 Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Glu
 Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn
 Ile Val Thr Asp Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro
 5 Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile
 Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
 Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys
 Val Leu Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys
 Tyr His Ser Asn Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro
 10 Val Val Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys
 Gly Glu Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln
 Leu Asp Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His
 Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly
 Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val
 15 Lys Thr Ile His Thr Asp Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
 Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro
 Tyr Asn Pro Gln Ser Gln Gly Val Val Glu Ser Met Asn Lys Glu Leu
 Lys Lys Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr
 Ala Val Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly
 20 Ile Gly Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr
 Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn
 Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu Trp Lys Gly Pro
 Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn
 Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
 25 Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp
 Glu Asp (SEQ ID NO:2) .

The present invention especially relates to an adenoviral vector vaccine which
 comprises a codon optimized HIV-1 DNA pol construct wherein, in addition to
 deletion of the portion of the wild type sequence encoding the protease activity, a
 30 combination of active site residue mutations are introduced which are deleterious to
 HIV-1 pol (RT-RH-IN) activity of the expressed protein. Therefore, the present
 invention preferably relates to an adenoviral HIV-1 DNA pol-based vaccine wherein
 the construct is devoid of DNA sequences encoding any PR activity, as well as
 containing a mutation(s) which at least partially, and preferably substantially,
 35 abolishes RT, RNase and/or IN activity. One type of HIV-1 pol mutant which is part
 and parcel of an adenoviral vector vaccine may include but is not limited to a mutated

DNA molecule comprising at least one nucleotide substitution which results in a point mutation which effectively alters an active site within the RT, RNase and/or IN regions of the expressed protein, resulting in at least substantially decreased enzymatic activity for the RT, RNase H and/or IN functions of HIV-1 Pol. In a preferred embodiment of this portion of the invention, a HIV-1 DNA pol construct contains a mutation or mutations within the Pol coding region which effectively abolishes RT, RNase H and IN activity. An especially preferable HIV-1 DNA pol construct in a DNA molecule which contains at least one point mutation which alters the active site of the RT, RNase H and IN domains of Pol, such that each activity is at least substantially abolished. Such a HIV-1 Pol mutant will most likely comprise at least one point mutation in or around each catalytic domain responsible for RT, RNase H and IN activity, respectfully. To this end, an especially preferred HIV-1 DNA pol construct is exemplified herein and contains nine codon substitution mutations which results in an inactivated Pol protein (IA Pol: SEQ ID NO:4, Figure 17A-C) which has no PR, RT, RNase or IN activity, wherein three such point mutations reside within each of the RT, RNase and IN catalytic domains. Therefore, an especially preferred exemplification is an adenoviral vaccine which comprises, in an appropriate fashion, a DNA molecule which encodes IA-pol, which contains all nine mutations as shown below in Table 1. An additional preferred amino acid residue for substitution is Asp551, localized within the RNase domain of Pol. Any combination of the mutations disclosed herein may suitable and therefore may be utilized as an IA-Pol-based vaccine of the present invention. While addition and deletion mutations are contemplated and within the scope of the invention, the preferred mutation is a point mutation resulting in a substitution of the wild type amino acid with an alternative amino acid residue.

Table 1

	<u>wt aa</u>	<u>aa residue</u>	<u>mutant aa</u>	<u>enzyme function</u>
	Asp	112	Ala	RT
	Asp	187	Ala	RT
30	Asp	188	Ala	RT
	Asp	445	Ala	RNase H
	Glu	480	Ala	RNase H
	Asp	500	Ala	RNase H
	Asp	626	Ala	IN
35	Asp	678	Ala	IN
	Glu	714	Ala	IN

It is preferred that point mutations be incorporated into the IAPol mutant adenoviral vaccines of the present invention so as to lessen the possibility of altering epitopes in and around the active site(s) of HIV-1 Pol.

To this end, SEQ ID NO:3 discloses the nucleotide sequence which codes for a codon optimized pol in addition to the nine mutations shown in Table 1, disclosed as follows, and referred to herein as "IAPol":

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AGATCTACCA TGGCCCCCAT CTCCCCCATT GAGACTGTGC CTGTGAAGCT GAAGCCTGGC
ATGGATGGCC CCAAGGTGAA GCAGTGGCCC CTGACTGAGG AGAAGATCAA GGCCCTGGTG
GAAATCTGCA CTGAGATGGA GAAGGAGGGC AAAATCTCCA AGATTGGCCC CGAGAACCCC
10 TACAACACCC CTGTGTTTGC CATCAAGAAG AAGGACTCCA CCAAGTGGAG GAAGCTGGTG
GACTTCAGGG AGCTGAACAA GAGGACCCAG GACTTCTGGG AGGTGCAGCT GGGCATCCCC
CACCCCGCTG GCCTGAAGAA GAAGAAGTCT GTGACTGTGC TGGCTGTGGG GGATGCCTAC
TTCTCTGTGC CCCTGGATGA GGACTTCAGG AAGTACACTG CCTTCACCAT CCCCTCCATC
AACAATGAGA CCCCTGGCAT CAGGTACCAG TACAATGTGC TGCCCCAGGG CTGGAAGGGC
15 TCCCTTGCCA TCTTCCAGTC CTCCATGACC AAGATCCTGG AGCCCTTCAG GAAGCAGAAC
CCTGACATTG TGATCTACCA GTACATGGCT GCCCTGTATG TGGGCTCTGA CCTGGAGATT
TGGCAGCACA GGACCAAGAT TGAGGAGCTG AGGCAGCACC TGCTGAGGTG GGGCCTGACC
ACCCCTGACA AGAAGCACCA GAAGGAGCCC CCCTTCCTGT GGATGGGCTA TGAGCTGCAC
CCCGACAAGT GGACTGTGCA GCCCATTGTG CTGCCTGAGA AGGACTCCTG GACTGTGAAT
20 GACATCCAGA AGCTGGTGGG CAAGCTGAAC TGGGCCTCCC AAATCTACCC TGGCATCAAG
GTGAGGCAGC TGTGCAAGCT GCTGAGGGGC ACCAAGGCCC TGAAGTGGT GATCCCCCTG
ACTGAGGAGG CTGAGCTGGA GCTGGCTGAG AACAGGGAGA TCCTGAAGGA GCCTGTGCAT
GGGGTGTAAT ATGACCCCTC CAAGGACCTG ATTGCTGAGA TCCAGAAGCA GGGCCAGGGC
CAGTGGACCT ACCAAATCTA CCAGGAGCCC TTCAAGAACC TGAAGACTGG CAAGTATGCC
25 AGGATGAGGG GGGCCACAC CAATGATGTG AAGCAGCTGA CTGAGGCTGT GCAGAAGATC
ACCACTGAGT CCATTGTGAT CTGGGGCAAG ACCCCCAAGT TCAAGCTGCC CATCCAGAAG
GAGACCTGGG AGACCTGGTG GACTGAGTAC TGGCAGGCCA CCTGGATCCC TGAGTGGGAG
TTTGTGAACA CCCCCCCCCT GGTGAAGCTG TGGTACCAGC TGGAGAAGGA GCCCATTGTG
GGGCTGAGA CCTTCTATGT GGCTGGGGCT GCCAACAGGG AGACCAAGCT GGGCAAGGCT
30 GGCTATGTGA CCAACAGGGG CAGGCAGAAG GTGGTGACCC TGAAGTACAC CACCAACCAG
AAGACTGCCC TCCAGGCCAT CTACCTGGCC CTCCAGGACT CTGGCCTGGA GGTGAACATT
GTGACTGCCT CCCAGTATGC CCTGGGCATC ATCCAGGCCC AGCCTGATCA GTCTGAGTCT
GAGCTGGTGA ACCAGATCAT TGAGCAGCTG ATCAAGAAGG AGAAGGTGTA CCTGGCCTGG
GTGCTGCCCC ACAAGGGCAT TGGGGCAAT GAGCAGGTGG ACAAGCTGGT GTCTGTCTGGC
35 ATCAGGAAGG TGCTGTTTCT GGATGGCATT GACAAGGCCC AGGATGAGCA TGAGAAGTAC
CACTCCAAC TGGAGGGCTAT GGCCTCTGAC TTCAACCTGC CCCCTGTGGT GGCTAAGGAG

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ATTGTGGCCT CCTGTGACAA GTGCCAGCTG AAGGGGGAGG CCATGCATGG GCAGGTGGAC
 TGCTCCCCTG GCATCTGGCA GCTGGCCTGC ACCCACCTGG AGGGCAAGGT GATCCTGGTG
 GCTGTGCATG TGGCCTCCGG CTACATTGAG GCTGAGGTGA TCCCTGCTGA GACAGGCCAG
 GAGACTGCCT ACTTCCTGCT GAAGCTGGCT GGCAGGTGGC CTGTGAAGAC CATCCACACT
 5 GCCAATGGCT CCAACTTCAC TGGGGCCACA GTGAGGGCTG CCTGCTGGTG GGCTGGCATC
 AAGCAGGAGT TTGGCATCCC CTACAACCCC CAGTCCCAGG GGGTGGTGGC CTCCATGAAC
 AAGGAGCTGA AGAAGATCAT TGGGCAGGTG AGGGACCAGG CTGAGCACCT GAAGACAGCT
 GTGCAGATGG CTGTGTTTCT CCACAACCTT AAGAGGAAGG GGGGCATCGG GGGCTACTCC
 GCTGGGGAGA GGATTGTGGA CATCATTGCC ACAGACATCC AGACCAAGGA GCTCCAGAAG
 10 CAGATCACCA AGATCCAGAA CTTGAGGGTG TACTACAGGG ACTCCAGGAA CCCCCTGTGG
 AAGGGCCCTG CCAAGCTGCT GTGGAAGGGG GAGGGGGCTG TGGTGATCCA GGACAACTCT
 GACATCAAGG TGGTGCCAG GAGGAAGGCC AAGATCATCA GGGACTATGG CAAGCAGATG
 GCTGGGGATG ACTGTGTGGC CTCCAGGCAG GATGAGGACT AAAGCCCGGG CAGATCT (SEQ ID
 NO:3).

15 In order to produce the IA-pol-based adenoviral vaccines of the present
 invention, inactivation of the enzymatic functions was achieved by replacing a total of
 nine active site residues from the enzyme subunits with alanine side-chains. As
 shown in Table 1, all residues that comprise the catalytic triad of the polymerase,
 namely Asp112, Asp187, and Asp188, were substituted with alanine (Ala) residues
 20 (Larder, et al., *Nature* 1987, 327: 716-717; Larder, et al., 1989, *Proc. Natl. Acad. Sci.*
 1989, 86: 4803-4807). Three additional mutations were introduced at Asp445,
 Glu480 and Asp500 to abolish RNase H activity (Asp551 was left unchanged in this
 IA Pol construct), with each residue being substituted for an Ala residue, respectively
 (Davies, et al., 1991, *Science* 252:, 88-95; Schatz, et al., 1989, *FEBS Lett.* 257: 311-
 25 314; Mizrahi, et al., 1990, *Nucl. Acids. Res.* 18: pp. 5359-5353). HIV pol integrase
 function was abolished through three mutations at Asp626, Asp678 and Glu714.
 Again, each of these residues has been substituted with an Ala residue (Wiskerchen,
 et al., 1995, *J. Virol.* 69: 376-386; Leavitt, et al., 1993, *J. Biol. Chem.* 268: 2113-
 2119). Amino acid residue Pro3 of SEQ ID NO:4 marks the start of the RT gene.
 30 The complete amino acid sequence of IA-Pol is disclosed herein as SEQ ID NO:4 and
 Figure 17A-C, as follows:

Met Ala Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro
 Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys
 Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys
 35 Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala
 Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg

Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile
 Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Ala
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys
 Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile
 5 Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala
 Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln
 Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Ala Ala Leu Tyr Val Gly
 Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu Arg
 Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His Gln
 10 Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys
 Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
 Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile
 Tyr Pro Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr
 Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu
 15 Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr
 Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln
 Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys
 Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys
 Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile
 20 Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
 Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp
 Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu
 Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Ala Gly Ala Ala
 Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly
 25 Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Ala
 Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn
 Ile Val Thr Ala Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro
 Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile
 Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
 30 Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys
 Val Leu Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys
 Tyr His Ser Asn Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro
 Val Val Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys
 Gly Glu Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln
 35 Leu Ala Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His
 Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly

Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val
 Lys Thr Ile His Thr Ala Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
 Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro
 Tyr Asn Pro Gln Ser Gln Gly Val Val Ala Ser Met Asn Lys Glu Leu
 5 Lys Lys Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr
 Ala Val Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly
 Ile Gly Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr
 Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn
 Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu Trp Lys Gly Pro
 10 Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn
 Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
 Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp
 Glu Asp (SEQ ID NO:4) .

As noted above, it will be understood that any combination of the mutations
 15 disclosed above may be suitable and therefore be utilized as an IA-pol-based
 adenoviral HIV vaccine of the present invention, either when administered alone or in
 a combined modality regime and/or a prime-boost regimen. For example, it may be
 possible to mutate only 2 of the 3 residues within the respective reverse transcriptase,
 RNase-H, and integrase coding regions while still abolishing these enzymatic
 20 activities. However, the IA-pol construct described above and disclosed as SEQ ID
 NO:3, as well as the expressed protein (SEQ ID NO:4;) is preferred. It is also
 preferred that at least one mutation be present in each of the three catalytic domains.

Another aspect of this portion of the invention are codon optimized HIV-1
 Pol-based vaccine constructions which comprise a eukaryotic trafficking signal
 25 peptide such as from tPA (tissue-type plasminogen activator) or by a leader peptide
 such as is found in highly expressed mammalian proteins such as immunoglobulin
 leader peptides. Any functional leader peptide may be tested for efficacy. However,
 a preferred embodiment of the present invention, as with HIV-1 Nef constructs shown
 herein, is to provide for a HIV-1 Pol mutant adenoviral vaccine construction wherein
 30 the pol coding region or a portion thereof is operatively linked to a leader peptide,
 preferably a leader peptide from human tPA. In other words, a codon optimized
 HIV-1 Pol mutant such as IA-Pol (SEQ ID NO:4) may also comprise a leader peptide
 at the amino terminal portion of the protein, which may effect cellular trafficking and
 hence, immunogenicity of the expressed protein within the host cell. As noted in
 35 Figure 16A-B, a DNA vector which may be utilized to practice the present invention
 may be modified by known recombinant DNA methodology to contain a leader signal

peptide of interest, such that downstream cloning of the modified HIV-1 protein of interest results in a nucleotide sequence which encodes a modified HIV-1 tPA/Pol protein. In the alternative, as noted above, insertion of a nucleotide sequence which encodes a leader peptide may be inserted into a DNA vector housing the open reading frame for the Pol protein of interest. Regardless of the cloning strategy, the end result is a polynucleotide vaccine which comprises vector components for effective gene expression in conjunction with nucleotide sequences which encode a modified HIV-1 Pol protein of interest, including but not limited to a HIV-1 Pol protein which contains a leader peptide. The amino acid sequence of the human tPA leader utilized herein is as follows: MDAMKRGLCCVLLLCGAVFVSPSEISS (SEQ ID NO:17). Therefore, another aspect of the present invention is to generate HIV-1 Pol-based vaccine constructions which comprise a eukaryotic trafficking signal peptide such as from tPA. To this end, the present invention relates to a DNA molecule which encodes a codon optimized wt-pol DNA construct wherein the protease (PR) activity is deleted and a human tPA leader sequence is fused to the 5' end of the coding region. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:5, the open reading frame disclosed herein as SEQ ID NO:6.

To this end, the present invention relates to a DNA molecule which encodes a codon optimized wt-pol DNA construct wherein the protease (PR) activity is deleted and a human tPA leader sequence is fused to the 5' end of the coding region (herein, "tPA-wt-pol"). A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:5, the open reading frame being contained from an initiating Met residue at nucleotides 8-10 to a termination codon from nucleotides 2633-2635. SEQ ID NO:5 is as follows:

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25  GATCACCATG GATGCAATGA AGAGAGGGCT CTGCTGTGTG CTGCTGCTGT GTGGAGCAGT
    CTCGTTTTCG CCCAGCGAGA TCTCCGCCCC CATCTCCCCC ATTGAGACTG TGCCTGTGAA
    GCTGAAGCCT GGCATGGATG GCCCCAAGGT GAAGCAGTGG CCCCTGACTG AGGAGAAGAT
    CAAGGCCCTG GTGGAAATCT GCACTGAGAT GGAGAAGGAG GGCAAAATCT CCAAGATTGG
    CCCCAGAAAC CCCTACAACA CCCCTGTGTT TGCCATCAAG AAGAAGGACT CCACCAAGTG
30  GAGGAAGCTG GTGGACTTCA GGGAGCTGAA CAAGAGGACC CAGGACTTCT GGGAGGTGCA
    GCTGGGCATC CCCCACCCCG CTGGCCTGAA GAAGAAGAAG TCTGTGACTG TGCTGGATGT
    GGGGGATGCC TACTTCTCTG TGCCCCTGGA TGAGGACTTC AGGAAGTACA CTGCCTTCAC
    CATCCCCTCC ATCAACAATG AGACCCCTGG CATCAGGTAC CAGTACAATG TGCTGCCCCA
    GGGCTGGAAG GGCTCCCCTG CCATCTTCCA GTCCTCCATG ACCAAGATCC TGGAGCCCTT
35  CAGGAAGCAG AACCCTGACA TTGTGATCTA CCAGTACATG GATGACCTGT ATGTGGGCTC
    TGACCTGGAG ATTGGGCAGC ACAGGACCAA GATTGAGGAG CTGAGGCAGC ACCTGCTGAG

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GTGGGGCCTG ACCACCCCTG ACAAGAAGCA CCAGAAGGAG CCCCCCTTCC TGTGGATGGG
 CTATGAGCTG CACCCCGACA AGTGGACTGT GCAGCCCATT GTGCTGCCTG AGAAGGACTC
 CTGGACTGTG AATGACATCC AGAAGCTGGT GGGCAAGCTG AACTGGGCCT CCCAAATCTA
 CCCTGGCATC AAGGTGAGGC AGCTGTGCAA GCTGCTGAGG GGCACCAAGG CCCTGACTGA
 5 GGTGATCCCC CTGACTGAGG AGGCTGAGCT GGAGCTGGCT GAGAACAGGG AGATCCTGAA
 GGAGCCTGTG CATGGGGTGT ACTATGACCC CTCCAAGGAC CTGATTGCTG AGATCCAGAA
 GCAGGGCCAG GGCCAGTGGA CCTACCAAAT CTACCAGGAG CCCTTCAAGA ACCTGAAGAC
 TGGCAAGTAT GCCAGGATGA GGGGGGCCCA CACCAATGAT GTGAAGCAGC TGAAGGAGC
 TGTGCAGAAG ATCACCACCT AGTCCATTGT GATCTGGGGC AAGACCCCCA AGTTCAAGCT
 10 GCCCATCCAG AAGGAGACCT GGGAGACCTG GTGGACTGAG TACTGGCAGG CCACCTGGAT
 CCCTGAGTGG GAGTTTGTGA ACACCCCCCCT CCTGGTGAAG CTGTGGTACC AGCTGGAGAA
 GGAGCCCATT TTGGGGGCTG AGACCTTCTA TGTGGATGGG GCTGCCAACA GGGAGACCAA
 GCTGGGCAAG GCTGGCTATG TGACCAACAG GGGCAGGCAG AAGGTGGTGA CCCTGACTGA
 CACCACCAAC CAGAAGACTG AGCTCCAGGC CATCTACCTG GCCCTCCAGG ACTCTGGCCT
 15 GGAGGTGAAC ATTGTGACTG ACTCCCAGTA TGCCCTGGGC ATCATCCAGG CCCAGCCTGA
 TCAGTCTGAG TCTGAGCTGG TGAACCAGAT CATTGAGCAG CTGATCAAGA AGGAGAAGGT
 GTACCTGGCC TGGGTGCCTG CCCACAAGGG CATTGGGGGC AATGAGCAGG TGGACAAGCT
 GGTGTCTGCT GGCATCAGGA AGGTGCTGTT CCTGGATGGC ATTGACAAGG CCCAGGATGA
 GCATGAGAAG TACCACTCCA ACTGGAGGGC TATGGCCTCT GACTTCAACC TGCCCCCTGT
 20 GGTGGCTAAG GAGATTGTGG CCTCCTGTGA CAAGTGCCAG CTGAAGGGGG AGGCCATGCA
 TGGGCAGGTG GACTGCTCCC CTGGCATCTG GCAGCTGGAC TGCACCCACC TGGAGGGCAA
 GGTGATCCTG GTGGCTGTGC ATGTGGCCTC CGGCTACATT GAGGCTGAGG TGATCCCTGC
 TGAGACAGGC CAGGAGACTG CCTACTTCCT GCTGAAGCTG GCTGGCAGGT GGCCTGTGAA
 GACCATCCAC ACTGACAATG GCTCCAACCT CACTGGGGCC ACAGTGAGGG CTGCCTGCTG
 25 GTGGGCTGGC ATCAAGCAGG AGTTTGGCAT CCCCTACAAC CCCCAGTCCC AGGGGGTGGT
 GGAGTCCATG AACAAAGGAGC TGAAGAAGAT CATTGGGCAG GTGAGGGACC AGGCTGAGCA
 CCTGAAGACA GCTGTGCAGA TGGCTGTGTT CATCCACAAC TTCAAGAGGA AGGGGGGCAT
 CGGGGGCTAC TCCGCTGGGG AGAGGATTGT GGACATCATT GCCACAGACA TCCAGACCAA
 GGAGCTCCAG AAGCAGATCA CCAAGATCCA GAACTTCAGG GTGTACTACA GGGACTCCAG
 30 GAACCCCTG TGGAAGGGCC CTGCCAAGCT GCTGTGGAAG GGGGAGGGGG CTGTGGTGAT
 CCAGGACAAC TCTGACATCA AGGTGGTGCC CAGGAGGAAG GCCAAGATCA TCAGGGACTA
 TGGCAAGCAG ATGGCTGGGG ATGACTGTGT GGCCTCCAGG CAGGATGAGG ACTAAAGCCC
 GGGCAGATCT (SEQ ID NO:5).

The open reading frame of the wild type tPA-pol construct disclosed as SEQ
 35 ID NO:5 contains 875 amino acids, disclosed herein as SEQ ID NO:6, as follows:
 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly

Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ala Pro Ile Ser Pro Ile
 Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys Val
 Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile
 Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu
 5 Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr
 Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln
 Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His Pro Ala Gly Leu Lys
 Lys Lys Lys Ser Val Thr Val Leu Asp Val Gly Asp Ala Tyr Phe Ser
 Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr Ala Phe Thr Ile Pro
 10 Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr Asn Val Leu
 Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met Thr
 Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr
 Gln Tyr Met Asp Asp Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln
 His Arg Thr Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly
 15 Leu Thr Thr Pro Asp Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp
 Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Gln Pro Ile Val
 Leu Pro Glu Lys Asp Ser Trp Thr Val Asn Asp Ile Gln Lys Leu Val
 Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro Gly Ile Lys Val Arg
 Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu Val Ile
 20 Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu Ile
 Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu
 Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile
 Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met
 Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln
 25 Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro Lys Phe
 Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr Glu Tyr
 Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr Pro Pro
 Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val Gly Ala
 Glu Thr Phe Tyr Val Asp Gly Ala Ala Asn Arg Glu Thr Lys Leu Gly
 30 Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu
 Thr Asp Thr Thr Asn Gln Lys Thr Glu Leu Gln Ala Ile Tyr Leu Ala
 Leu Gln Asp Ser Gly Leu Glu Val Asn Ile Val Thr Asp Ser Gln Tyr
 Ala Leu Gly Ile Ile Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu
 Val Asn Gln Ile Ile Glu Gln Leu Ile Lys Lys Glu Lys Val Tyr Leu
 35 Ala Trp Val Pro Ala His Lys Gly Ile Gly Gly Asn Glu Gln Val Asp
 Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu Phe Leu Asp Gly Ile

Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn Trp Arg Ala
 Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile Val
 Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln
 Val Asp Cys Ser Pro Gly Ile Trp Gln Leu Asp Cys Thr His Leu Glu
 5 Gly Lys Val Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu
 Ala Glu Val Ile Pro Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu
 Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Thr Ile His Thr Asp Asn
 Gly Ser Asn Phe Thr Gly Ala Thr Val Arg Ala Ala Cys Trp Trp Ala
 Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn Pro Gln Ser Gln Gly
 10 Val Val Glu Ser Met Asn Lys Glu Leu Lys Lys Ile Ile Gly Gln Val
 Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val Phe
 Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly
 Glu Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu
 Gln Lys Gln Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp
 15 Ser Arg Asn Pro Leu Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly
 Glu Gly Ala Val Val Ile Gln Asp Asn Ser Asp Ile Lys Val Val Pro
 Arg Arg Lys Ala Lys Ile Ile Arg Asp Tyr Gly Lys Gln Met Ala Gly
 Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp (SEQ ID NO:6).

The present invention also relates to a codon optimized HIV-1 Pol mutant
 20 contained within a recombinant adenoviral vector such as IA-Pol (SEQ ID NO:4)
 which comprises a leader peptide at the amino terminal portion of the protein, which
 may effect cellular trafficking and hence, immunogenicity of the expressed protein
 within the host cell. Any such adenoviral-based HIV-1 DNA pol mutant disclosed in
 the above paragraphs is suitable for fusion downstream of a leader peptide, such as a
 25 leader peptide including but not limited to the human tPA leader sequence. Therefore,
 any such leader peptide-based HIV-1 pol mutant construct may include but is not
 limited to a mutated DNA molecule which effectively alters the catalytic activity of
 the RT, RNase and/or IN region of the expressed protein, resulting in at least
 substantially decreased enzymatic activity one or more of the RT, RNase H and/or IN
 30 functions of HIV-1 Pol. In a preferred embodiment of this portion of the invention, a
 leader peptide/HIV-1 DNA pol construct contains a mutation or mutations within the
 Pol coding region which effectively abolishes RT, RNase H and IN activity. An
 especially preferable HIV-1 DNA pol construct is a DNA molecule which contains at
 least one point mutation which alters the active site and catalytic activity within the
 35 RT, RNase H and IN domains of Pol, such that each activity is at least substantially
 abolished, and preferably totally abolished. Such a HIV-1 Pol mutant will most likely

comprise at least one point mutation in or around each catalytic domain responsible for RT, RNase H and IN activity, respectfully. An especially preferred embodiment of this portion of the invention relates to a human tPA leader fused to the IA-Pol protein comprising the nine mutations shown in Table 1. The DNA molecule is disclosed
 5 herein as SEQ ID NO:7 and the expressed tPA-IA Pol protein comprises a fusion junction as shown in Figure 18. The complete amino acid sequence of the expressed protein is set forth in SEQ ID NO:8. To this end, SEQ ID NO:7 discloses the nucleotide sequence which codes for a human tPA leader fused to the IA Pol protein comprising the nine mutations shown in Table 1 (herein, "tPA-opt-IApol"). The open
 10 reading frame begins with the initiating Met (nucleotides 8-10) and terminates with a "TAA" codon at nucleotides 2633-2635. The nucleotide sequence encoding tPA-IAPol is also disclosed as follows:

GATCACCATG GATGCAATGA AGAGAGGGCT CTGCTGTGTG CTGCTGCTGT GTGGAGCAGT
 CTTCGTTTCG CCCAGCGAGA TCTCCGCCCC CATCTCCCCC ATTGAGACTG TGCCTGTGAA
 15 GCTGAAGCCT GGCATGGATG GCCCCAAGGT GAAGCAGTGG CCCCTGACTG AGGAGAAGAT
 CAAGGCCCTG GTGGAAATCT GCACTGAGAT GGAGAAGGAG GGCAAAATCT CCAAGATTGG
 CCCCAGAAAC CCCTACAACA CCCCTGTGTT TGCCATCAAG AAGAAGGACT CCACCAAGTG
 GAGGAAGCTG GTGGACTTCA GGGAGCTGAA CAAGAGGACC CAGGACTTCT GGGAGGTGCA
 GCTGGGCATC CCCCACCCCG CTGGCCTGAA GAAGAAGAAG TCTGTGACTG TGCTGGCTGT
 20 GGGGGATGCC TACTTCTCTG TGCCCTGGA TGAGGACTTC AGGAAGTACA CTGCCTTCAC
 CATCCCCCTC ATCAACAATG AGACCCCTGG CATCAGGTAC CAGTACAATG TGCTGCCCCA
 GGGCTGGAAG GGCTCCCTG CCATCTTCCA GTCTCCATG ACCAAGATCC TGGAGCCCTT
 CAGGAAGCAG AACCCCTGACA TTGTGATCTA CCAGTACATG GCTGCCCTGT ATGTGGGCTC
 TGACCTGGAG ATTGGGCAGC ACAGGACCAA GATTGAGGAG CTGAGGCAGC ACCTGCTGAG
 25 GTGGGGCCTG ACCACCCCTG ACAAGAAGCA CCAGAAGGAG CCCCCCTTCC TGTGGATGGG
 CTATGAGCTG CACCCCGACA AGTGGACTGT GCAGCCATT GTGCTGCCTG AGAAGGACTC
 CTGGACTGTG AATGACATCC AGAAGCTGGT GGGCAAGCTG AACTGGGCCT CCCAAATCTA
 CCCTGGCATC AAGGTGAGGC AGCTGTGCAA GCTGCTGAGG GGCACCAAGG CCCTGACTGA
 GGTGATCCCC CTGACTGAGG AGGCTGAGCT GGAGCTGGCT GAGAACAGGG AGATCCTGAA
 30 GGAGCCTGTG CATGGGGTGT ACTATGACCC CTCCAAGGAC CTGATTGCTG AGATCCAGAA
 GCAGGGCCAG GGCCAGTGGA CCTACCAAAT CTACCAGGAG CCCTTCAAGA ACCTGAAGAC
 TGGCAAGTAT GCCAGGATGA GGGGGGCCCA CACCAATGAT GTGAAGCAGC TGACTGAGGC
 TGTGCAGAAG ATCACCCTG AGTCCATTGT GATCTGGGGC AAGACCCCCA AGTTCAAGCT
 GCCCATCCAG AAGGAGACCT GGGAGACCTG GTGGACTGAG TACTGGCAGG CCACCTGGAT
 35 CCCTGAGTGG GAGTTTGTGA ACACCCCCC CCTGGTGAAG CTGTGGTACC AGCTGGAGAA
 GGAGCCCAT TGTGGGGCTG AGACCTTCTA TGTGGCTGGG GCTGCCAACA GGGAGACCAA

GCTGGGCAAG GCTGGCTATG TGACCAACAG GGGCAGGCAG AAGGTGGTGA CCCTGACTGA
 CACCACCAAC CAGAAGACTG CCCTCCAGGC CATCTACCTG GCCCTCCAGG ACTCTGGCCT
 GGAGGTGAAC ATTGTGACTG CCTCCAGTA TGCCCTGGGC ATCATCCAGG CCCAGCCTGA
 TCAGTCTGAG TCTGAGCTGG TGAACCAGAT CATTGAGCAG CTGATCAAGA AGGAGAAGGT
 5 GTACCTGGCC TGGGTGCCTG CCCACAAGGG CATTGGGGGC AATGAGCAGG TGGACAAGCT
 GGTGTCTGCT GGCATCAGGA AGGTGCTGTT CCTGGATGGC ATTGACAAGG CCCAGGATGA
 GCATGAGAAG TACCACTCCA ACTGGAGGGC TATGGCCTCT GACTTCAACC TGCCCCCTGT
 GGTGGCTAAG GAGATTGTGG CCTCCTGTGA CAAGTGCCAG CTGAAGGGGG AGGCCATGCA
 TGGGCAGGTG GACTGCTCCC CTGGCATCTG GCAGCTGGCC TGCACCCACC TGGAGGGCAA
 10 GGTGATCCTG GTGGCTGTGC ATGTGGCCTC CGGCTACATT GAGGCTGAGG TGATCCCTGC
 TGAGACAGGC CAGGAGACTG CCTACTTCCT GCTGAAGCTG GCTGGCAGGT GGCCTGTGAA
 GACCATCCAC ACTGCCAATG GCTCCAACCT CACTGGGGCC ACAGTGAGGG CTGCCTGCTG
 GTGGGCTGGC ATCAAGCAGG AGTTTGGCAT CCCCTACAAC CCCCAGTCCC AGGGGGTGGT
 GGCCTCCATG AACAAGGAGC TGAAGAAGAT CATTGGGCAG GTGAGGGACC AGGCTGAGCA
 15 CCTGAAGACA GCTGTGCAGA TGGCTGTGTT CATCCACAAC TTCAAGAGGA AGGGGGGCAT
 CGGGGGCTAC TCCGCTGGGG AGAGGATTGT GGACATCATT GCCACAGACA TCCAGACCAA
 GGAGCTCCAG AAGCAGATCA CCAAGATCCA GAACTTCAGG GTGTACTACA GGGACTCCAG
 GAACCCCTG TGGGAAGGGCC CTGCCAAGCT GCTGTGGAAG GGGGAGGGGG CTGTGGTGAT
 CCAGGACAAC TCTGACATCA AGGTGGTGCC CAGGAGGAAG GCCAAGATCA TCAGGGACTA
 20 TGGCAAGCAG ATGGCTGGGG ATGACTGTGT GGCCTCCAGG CAGGATGAGG ACTAAAGCCC
 GGGCAGATCT (SEQ ID NO:7).

The open reading frame of the tPA-IA-pol construct disclosed as SEQ ID NO:7 contains 875 amino acids, disclosed herein as tPA-IA-Pol and SEQ ID NO:8, as follows:

25 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ala Pro Ile Ser Pro Ile
 Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys Val
 Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile
 Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu
 30 Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr
 Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln
 Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His Pro Ala Gly Leu Lys
 Lys Lys Lys Ser Val Thr Val Leu Ala Val Gly Asp Ala Tyr Phe Ser
 Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr Ala Phe Thr Ile Pro
 35 Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr Asn Val Leu
 Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met Thr

Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr
 Gln Tyr Met Ala Ala Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln
 His Arg Thr Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly
 Leu Thr Thr Pro Asp Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp
 5 Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Gln Pro Ile Val
 Leu Pro Glu Lys Asp Ser Trp Thr Val Asn Asp Ile Gln Lys Leu Val
 Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro Gly Ile Lys Val Arg
 Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu Val Ile
 Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu Ile
 10 Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu
 Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile
 Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met
 Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln
 Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro Lys Phe
 15 Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr Glu Tyr
 Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr Pro Pro
 Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val Gly Ala
 Glu Thr Phe Tyr Val Ala Gly Ala Ala Asn Arg Glu Thr Lys Leu Gly
 Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu
 20 Thr Asp Thr Thr Asn Gln Lys Thr Ala Leu Gln Ala Ile Tyr Leu Ala
 Leu Gln Asp Ser Gly Leu Glu Val Asn Ile Val Thr Ala Ser Gln Tyr
 Ala Leu Gly Ile Ile Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu
 Val Asn Gln Ile Ile Glu Gln Leu Ile Lys Lys Glu Lys Val Tyr Leu
 Ala Trp Val Pro Ala His Lys Gly Ile Gly Gly Asn Glu Gln Val Asp
 25 Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu Phe Leu Asp Gly Ile
 Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn Trp Arg Ala
 Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile Val
 Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln
 Val Asp Cys Ser Pro Gly Ile Trp Gln Leu Ala Cys Thr His Leu Glu
 30 Gly Lys Val Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu
 Ala Glu Val Ile Pro Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu
 Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Thr Ile His Thr Ala Asn
 Gly Ser Asn Phe Thr Gly Ala Thr Val Arg Ala Ala Cys Trp Trp Ala
 Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn Pro Gln Ser Gln Gly
 35 Val Val Ala Ser Met Asn Lys Glu Leu Lys Lys Ile Ile Gly Gln Val
 Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val Phe

Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly
 Glu Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu
 Gln Lys Gln Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp
 Ser Arg Asn Pro Leu Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly
 5 Glu Gly Ala Val Val Ile Gln Asp Asn Ser Asp Ile Lys Val Val Pro
 Arg Arg Lys Ala Lys Ile Ile Arg Asp Tyr Gly Lys Gln Met Ala Gly
 Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp (SEQ ID NO:8).

EXAMPLE 18

10 CODON OPTIMIZED HIV-1 NEF AND CODON OPTIMIZED HIV-1 NEF MODIFICATIONS

Codon optimized version of HIV-1 Nef and HIV-1 Nef modifications are essentially as described in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed
 15 December 15, 2000, both documents which are hereby incorporated by reference. As disclosed within the above-mentioned documents, particular embodiments of codon optimized Nef and Nef modifications relate to a DNA molecule encoding HIV-1 Nef from the HIV-1 jf1 isolate wherein the codons are optimized for expression in a mammalian system such as a human. The DNA molecule which encodes this protein
 20 is disclosed herein as SEQ ID NO:9, while the expressed open reading frame is disclosed herein as SEQ ID NO:10. Another embodiment of Nef-based coding regions for use in the adenoviral vectors of the present invention comprise a codon optimized DNA molecule encoding a protein containing the human plasminogen activator (tpa) leader peptide fused with the NH₂-terminus of the HIV-1 Nef
 25 polypeptide. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:11, while the expressed open reading frame is disclosed herein as SEQ ID NO:12. Another modified Nef optimized coding region relates to a DNA molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and
 30 substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175, herein described as opt nef (G2A, LLAA). The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:13, while the expressed open reading frame is disclosed herein as SEQ ID NO:14. An additional embodiment relates to a DNA molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation
 35 site and dileucine motif have been deleted, as well as comprising a tPA leader peptide. This DNA molecule, opt tpanef (LLAA), comprises an open reading frame which

encodes a Nef protein containing a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef (jfrl), wherein Leu-174 and Leu-175 are substituted with Ala-174 and Ala-175, herein referred to as opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, while the expressed open reading frame is disclosed herein as SEQ ID NO:16.

5 As disclosed in the above-identified documents (U.S. Application Serial No. 09/738,782 and PCT International Application PCT/US00/34162) and reiterated herein, the following nef-based nucleotide and amino acid sequences which comprise the respective open reading frame are as follows:

1. The nucleotide sequence of the codon optimized version of HIV-1 jfrl
10 nef gene is disclosed herein as SEQ ID NO:9, as shown herein:

GATCTGCCAC CATGGGCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA
GGGAGAGGAT GAGGAGGGCC GAGCCC GCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG
CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCTCCA
ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG
15 GCTTCCCCGT GAGGCCCCAG GTGCCCCCTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC
TGTCCCACTT CCTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC
AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT
ACACCCCGG CCCC GG CATC AGGTTCCTCGG CTGGTGCTTC AAGCTGGTGC
CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAACTGC CTGCTGCACC
20 CCATGTCCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTGCACT
CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT
AAAGCCCGGG C (SEQ ID NO:9).

Preferred codon usage is as follows: Met (ATG), Gly (GGC), Lys (AAG),
Trp (TGG), Ser (TCC), Arg (AGG), Val (GTG), Pro (CCC), Thr (ACC), Glu (GAG);
25 Leu (CTG), His (CAC), Ile (ATC), Asn (AAC), Cys (TGC), Ala (GCC), Gln (CAG),
Phe (TTC) and Tyr (TAC). For an additional discussion relating to mammalian
(human) codon optimization, see WO 97/31115 (PCT/US97/02294), which is hereby
incorporated by reference. See also Figure 19A-B for a comparison of wild type vs.
codon optimized nucleotides comprising the open reading frame of HIV-Nef.

30 The open reading frame for SEQ ID NO:9 above comprises an initiating
methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides
660-662. The open reading frame of SEQ ID NO:9 provides for a 216 amino acid
HIV-1 Nef protein expressed through utilization of a codon optimized DNA vaccine
vector. The 216 amino acid HIV-1 Nef (jfrl) protein is disclosed herein as SEQ ID
35 NO:10, and as follows:

Met Gly Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val

Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg
 Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu
 Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp
 Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val
 5 Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp
 Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His
 Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln
 Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg
 Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro
 10 Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Leu Leu His
 Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu
 Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu
 His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:10).

HIV-1 Nef is a 216 amino acid cytosolic protein which associates with the
 15 inner surface of the host cell plasma membrane through myristylation of Gly-2
 (Franchini et al., 1986, *Virology* 155: 593-599). While not all possible Nef functions
 have been elucidated, it has become clear that correct trafficking of Nef to the inner
 plasma membrane promotes viral replication by altering the host intracellular
 environment to facilitate the early phase of the HIV-1 life cycle and by increasing the
 20 infectivity of progeny viral particles. In one aspect of the invention regarding
 codon-optimized, protein-modified polypeptides, the nef-encoding region of the
 adenovirus vector of the present invention is modified to contain a nucleotide
 sequence which encodes a heterologous leader peptide such that the amino terminal
 region of the expressed protein will contain the leader peptide. The diversity of
 25 function that typifies eukaryotic cells depends upon the structural differentiation of
 their membrane boundaries. To generate and maintain these structures, proteins must
 be transported from their site of synthesis in the endoplasmic reticulum to
 predetermined destinations throughout the cell. This requires that the trafficking
 proteins display sorting signals that are recognized by the molecular machinery
 30 responsible for route selection located at the access points to the main trafficking
 pathways. Sorting decisions for most proteins need to be made only once as they
 traverse their biosynthetic pathways since their final destination, the cellular location
 at which they perform their function, becomes their permanent residence.
 Maintenance of intracellular integrity depends in part on the selective sorting and
 35 accurate transport of proteins to their correct destinations. Defined sequence motifs
 exist in proteins which can act as 'address labels'. A number of sorting signals have

been found associated with the cytoplasmic domains of membrane proteins. An effective induction of CTL responses often required sustained, high level endogenous expression of an antigen. As membrane-association via myristylation is an essential requirement for most of Nef's function, mutants lacking myristylation, by glycine-to-
5 alanine change, change of the dileucine motif and/or by substitution with a tpa leader sequence as described herein, will be functionally defective, and therefore will have improved safety profile compared to wild-type Nef for use as an HIV-1 vaccine component.

In another embodiment of this portion of the invention, either the DNA vector
10 or the HIV-1 nef nucleotide sequence is modified to include the human tissue-specific plasminogen activator (tPA) leader. As shown in Figure 16A-B, a DNA vector may be modified by known recombinant DNA methodology to contain a leader signal peptide of interest, such that downstream cloning of the modified HIV-1 protein of interest results in a nucleotide sequence which encodes a modified HIV-1 tPA/Nef
15 protein. In the alternative, as noted above, insertion of a nucleotide sequence which encodes a leader peptide may be inserted into a DNA vector housing the open reading frame for the Nef protein of interest. Regardless of the cloning strategy, the end result is a polynucleotide vaccine which comprises vector components for effective gene expression in conjunction with nucleotide sequences which encode a modified HIV-1
20 Nef protein of interest, including but not limited to a HIV-1 Nef protein which contains a leader peptide. The amino acid sequence of the human tPA leader utilized herein is as follows: MDAMKRGLCCVLLLCGAVFVSPSEISS (SEQ ID NO:17).

It has been shown that myristylation of Gly-2 in conjunction with a dileucine motif in the carboxy region of the protein is essential for Nef-induced down
25 regulation of CD4 (Aiken et al., 1994, *Cell* 76: 853-864) via endocytosis. It has also been shown that Nef expression promotes down regulation of MHCI (Schwartz et al., 1996, *Nature Medicine* 2(3): 338-342) via endocytosis. The present invention relates in part to DNA vaccines which encode modified Nef proteins altered in trafficking and/or functional properties. The modifications introduced into the adenoviral vector
30 HIV vaccines of the present invention include but are not limited to additions, deletions or substitutions to the nef open reading frame which results in the expression of a modified Nef protein which includes an amino terminal leader peptide, modification or deletion of the amino terminal myristylation site, and modification or deletion of the dileucine motif within the Nef protein and which alter
35 function within the infected host cell. Therefore, a central theme of the DNA molecules and recombinant adenoviral HIV vaccines of the present invention is (1)

host administration and intracellular delivery of a codon optimized nef-based adenoviral HIV vaccine; (2) expression of a modified Nef protein which is immunogenic in terms of eliciting both CTL and Th responses; and, (3) inhibiting or at least altering known early viral functions of Nef which have been shown to promote HIV-1 replication and load within an infected host. Therefore, the nef coding region may be altered, resulting in a DNA vaccine which expresses a modified Nef protein wherein the amino terminal Gly-2 myristylation residue is either deleted or modified to express alternate amino acid residues. Also, the nef coding region may be altered so as to result in a DNA vaccine which expresses a modified Nef protein wherein the dileucine motif is either deleted or modified to express alternate amino acid residues. In addition, the adenoviral vector HIV vaccines of the present invention also relate to an isolated DNA molecule, regardless of codon usage, which expresses a wild type or modified Nef protein as described herein, including but not limited to modified Nef proteins which comprise a deletion or substitution of Gly 2, a deletion or substitution of Leu 174 and Leu 175 and/or inclusion of a leader sequence.

Therefore, specific Nef-based constructs further include the following, as exemplification's and not limitations. For example, the present invention relates to an adenoviral vector vaccine which encodes modified forms of HIV-1, an open reading frame which encodes a Nef protein which comprises a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef (jfr1) is referred to herein as opt tpanef. The nucleotide sequence comprising the open reading frame of opt tpanef is disclosed herein as SEQ ID NO:11, as shown below:

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CATGGATGCA ATGAAGAGAG GGCTCTGCTG TGTGCTGCTG CTGTGTGGAG CAGTCTTCGT
TTCGCCCAGC GAGATCTCCT CCAAGAGGTC CGTGCCCGGC TGGTCCACCG TGAGGGAGAG
GATGAGGAGG GCCGAGCCCG CCGCCGACAG GGTGAGGAGG ACCGAGCCCG CCGCCGTGGG
CGTGCGCGCC GTGTCCAGGG ACCTGGAGAA GCACGGCGCC ATCACCTCCT CCAACACCGC
CGCCACCAAC GCCGACTGCG CCTGGCTGGA GGCCAGGAG GACGAGGAGG TGGGCTTCCC
CGTGAGGCCC CAGGTGCCCC TGAGGCCCAT GACCTACAAG GGCGCCGTGG ACCTGTCCCA
CTTCCTGAAG GAGAAGGGCG GCCTGGAGGG CCTGATCCAC TCCAGAAGA GGCAGGACAT
CCTGGACCTG TGGGTGTACC ACACCCAGGG CTACTTCCCC GACTGGCAGA ACTACACCCC
CGGCCCCGGC ATCAGGTTC CCGTACCTT CGGCTGGTGC TTCAAGCTGG TGCCCGTGGG
GCCCAGAGAAG GTGGAGGAGG CCAACGAGGG CGAGAACAAC TGCCTGCTGC ACCCATGTG
CCAGCACGGC ATCGAGGACC CCGAGAAGGA GGTGCTGGAG TGGAGGTTTCG ACTCCAAGCT
GGCCTTCCAC CACGTGGCCA GGGAGCTGCA CCCCAGGTAC TACAAGGACT GCTAAAGCC
(SEQ ID NO:11).

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The open reading frame for SEQ ID NO:11 comprises an initiating methionine

residue at nucleotides 2-4 and a "TAA" stop codon from nucleotides 713-715. The open reading frame of SEQ ID NO:3 provides for a 237 amino acid HIV-1 Nef protein which comprises a tPA leader sequence fused to amino acids 6-216 of HIV-1 Nef, including the dileucine motif at amino acid residues 174 and 175. This 237 amino acid tPA/Nef (jfrl) fusion protein is disclosed herein as SEQ ID NO:12, and is shown as follows:

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ser Lys Arg Ser Val Pro
 Gly Trp Ser Thr Val Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala
 10 Asp Arg Val Arg Arg Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val
 Ser Arg Asp Leu Glu Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala
 Ala Thr Asn Ala Asp Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu
 Val Gly Phe Pro Val Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr
 Lys Gly Ala Val Asp Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu
 15 Glu Gly Leu Ile His Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp
 Val Tyr His Thr Gln Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro
 Gly Pro Gly Ile Arg Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu
 Val Pro Val Glu Pro Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn
 Asn Cys Leu Leu His Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu
 20 Lys Glu Val Leu Glu Trp Arg Phe Asp Ser Lys Leu Ala Phe His His
 Val Ala Arg Glu Leu His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:12).

Therefore, this exemplified Nef protein, Opt tPA-Nef, contains both a tPA leader sequence as well as deleting the myristylation site of Gly-2A DNA molecule encoding HIV-1 Nef from the HIV-1 jfrl isolate wherein the codons are optimized for expression in a mammalian system such as a human.

In another specific embodiment of the present invention, a DNA molecule is disclosed which encodes optimized HIV-1 Nef wherein the open reading frame of a recombinant adenoviral HIV vaccine encodes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175. This open reading frame is herein described as opt nef (G2A,LLAA) and is disclosed as SEQ ID NO:13, which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662. The nucleotide sequence of this codon optimized version of HIV-1 jfrl nef gene with the above mentioned modifications is disclosed herein as SEQ ID NO:13, as follows:

GATCTGCCAC CATGGCCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA
 GGGAGAGGAT GAGGAGGGCC GAGCCCGCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG
 CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCCTCCA
 ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG
 5 GCTTCCCCGT GAGGCCCCAG GTGCCCCCTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC
 TGTCCTACTT CCTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC
 AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT
 ACACCCCCGG CCCCAGCATC AGGTTCCTCC TGACCTTCGG CTGGTGCTTC AAGCTGGTGC
 CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAACTGC GCCGCCACCC
 10 CCATGTCCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTCTACT
 CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT
 AAAGCCCCGGG C (SEQ ID NO:13).

The open reading frame of SEQ ID NO:13 encodes Nef (G2A,LLAA), disclosed herein as SEQ ID NO:14, as follows:

15 Met Ala Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val
 Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg
 Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu
 Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp
 Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val
 20 Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp
 Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His
 Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln
 Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg
 Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro
 25 Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Ala Ala His
 Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu
 Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu
 His Pro Glu Tyr Tyr Lys Asp Cys Ser (SEQ ID NO:14).

30 An additional embodiment of the present invention relates to another DNA
 molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation
 site and dileucine motif have been deleted, as well as comprising a tPA leader peptide.
 This DNA molecule, opt tpanef (LLAA) comprises an open reading frame which
 encodes a Nef protein containing a tPA leader sequence fused to amino acid residue
 6-216 of HIV-1 Nef (jfrl), wherein Leu-174 and Leu-175 are substituted with Ala-174
 35 and Ala-175 (Ala-195 and Ala-196 in this tPA-based fusion protein). The nucleotide

sequence comprising the open reading frame of opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, as shown below:

CATGGATGCA ATGAAGAGAG GGCTCTGCTG TGTGCTGCTG CTGTGTGGAG CAGTCTTCGT
 TTCGCCCAGC GAGATCTCCT CCAAGAGGTC CGTGCCCGGC TGGTCCACCG TGAGGGAGAG
 5 GATGAGGAGG GCCGAGCCCG CCGCCGACAG GGTGAGGAGG ACCGAGCCCG CCGCCGTGGG
 CGTGGGCGCC GTGTCCAGGG ACCTGGAGAA GCACGGCGCC ATCACCTCCT CCAACACCGC
 CGCCACCAAC GCCGACTGCG CCTGGCTGGA GGCCAGGAG GACGAGGAGG TGGGCTTCCC
 CGTGAGGCCC CAGGTGCCCC TGAGGCCCAT GACCTACAAG GGCGCCGTGG ACCTGTCCCA
 CTTCTGAAG GAGAAGGGCG GCCTGGAGGG CCTGATCCAC TCCCAGAAGA GGCAGGACAT
 10 CCTGGACCTG TGGGTGTACC ACACCCAGGG CTACTTCCCC GACTGGCAGA ACTACACCCC
 CGGCCCCGGC ATCAGGTTCC CCCTGACCTT CGGCTGGTGC TTCAAGCTGG TGCCCGTGGG
 GCCGAGAAG GTGGAGGAGG CCAACGAGGG CGAGAACAAC TGCGCCGCC ACCCATGTC
 CCAGCACGGC ATCGAGGACC CCGAGAAGGA GGTGCTGGAG TGGAGGTTCT ACTCCAAGCT
 GGCCTTCAC CACGTGGCCA GGGAGCTGCA CCCCAGTAC TACAAGGACT GCTAAAGCCC
 15 (SEQ ID NO:15).

The open reading frame of SEQ ID NO:7 encoding tPA-Nef (LLAA), disclosed herein as SEQ ID NO:16, is as follows:

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ser Lys Arg Ser Val Pro
 20 Gly Trp Ser Thr Val Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala
 Asp Arg Val Arg Arg Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val
 Ser Arg Asp Leu Glu Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala
 Ala Thr Asn Ala Asp Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu
 Val Gly Phe Pro Val Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr
 25 Lys Gly Ala Val Asp Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu
 Glu Gly Leu Ile His Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp
 Val Tyr His Thr Gln Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro
 Gly Pro Gly Ile Arg Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu
 Val Pro Val Glu Pro Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn
 30 Asn Cys Ala Ala His Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu
 Lys Glu Val Leu Glu Trp Arg Phe Asp Ser Lys Leu Ala Phe His His
 Val Ala Arg Glu Leu His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:16).

An adenoviral vector of the present invention may comprise a DNA sequence,
 regardless of codon usage, which expresses a wild type or modified Nef protein as
 35 described herein, including but not limited to modified Nef proteins which comprise a
 deletion or substitution of Gly 2, a deletion or substitution of Leu 174 and Leu 175

and/or inclusion of a leader sequence. Therefore, partial or fully codon optimized DNA vaccine expression vector constructs are preferred since such constructs should result in increased host expression. However, it is within the scope of the present invention to utilize "non-codon optimized" versions of the constructs disclosed herein, especially modified versions of HIV Nef which are shown to promote a substantial cellular immune response subsequent to host administration.

Figure 20A-C show nucleotide sequences at junctions between nef coding sequence and plasmid backbone of nef expression vectors V1Jns/nef (Figure 20A), V1Jns/nef(G2A,LLAA) (Figure 20B), V1Jns/tpanef (Figure 20C) and V1Jns/tpanef(LLAA) (Figure 20C, also). 5' and 3' flanking sequences of codon optimized nef or codon optimized nef mutant genes are indicated by bold/italic letters; nef and nef mutant coding sequences are indicated by plain letters. Also indicated (as underlined) are the restriction endonuclease sites involved in construction of respective nef expression vectors. V1Jns/tpanef and V1Jns/tpanef(LLAA) have identical sequences at the junctions.

Figure 21 shows a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine 174 and 175 are the sites involved in myristylation and dileucine motif, respectively.

EXAMPLE 19

MRKAd5Pol Construction and Virus Rescue

Construction of vector: shuttle plasmid and pre-adenovirus plasmid - Key steps performed in the construction of the vectors, including the pre-adenovirus plasmid denoted MRKAd5pol, is depicted in Figure 22. Briefly, the adenoviral shuttle vector for the full-length inactivated HIV-1 pol gene is as follows. The vector MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHPA(str.) is a derivative of the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. The vector contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*III site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1-/E3+)Cla1 (or MRKpAdHVE3) pre-plasmid. The vector, similar to the original shuttle vector contains the *Pac*I site, extension to the packaging signal region, and extension to the pIX gene. The synthetic full-length codon-optimized HIV-1 pol gene was isolated directly from the plasmid pV1Jns-HIV-pol-inact(opt). Digestion of this plasmid with *Bgl* II releases the pol

gene intact (comprising a codon optimized IA pol sequence as disclosed in SEQ ID NO:3). The pol fragment was gel purified and ligated into the MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHPA(str.) shuttle vector at the *Bgl*III site. The clones were checked for the correct orientation of the gene by using
 5 restriction enzymes *Dra*III/*Not*I. A positive clone was isolated and named MRKpdel+hCMVmin+FL-pol+bGHpA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows. Shuttle plasmid MRKpdel+hCMVmin+FL-pol+bGHpA(S) was digested with restriction enzymes *Pac*I and *Bst*1107 I (or its
 10 isoschizomer, *Bst*Z107 I) and then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla*I digested) adenoviral backbone plasmid, MRKpAd(E1-/E3+)*Cla*I. The resulting pre-plasmid originally named MRKpAd+hCMVmin+FL-pol+bGHpA(S)E3+ is now referred to as "pMRKAd5pol". The genetic structure of the resulting pMRKAd5pol was verified by PCR, restriction enzyme and DNA
 15 sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the pol transgene in transient transfection cell culture. The complete nucleotide sequence of this pMRKAd5HIV-1pol adenoviral vector is shown in Figure 26 A-AO.

20 *Generation of research-grade recombinant adenovirus* - The pre-adenovirus plasmid, pMRKAd5pol, was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAd5pol was digested with restriction enzyme *Pac*I (New England Biolabs) and 3.3 µg was transfected per 6 cm dish of PER.C6[®] cells using the calcium phosphate co-
 25 precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech Inc.). *Pac*I digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested 6 -10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at ≤ -60°C. This pol containing
 30 recombinant adenovirus is referred to herein as "MRKAd5pol". This recombinant adenovirus expresses an inactivated HIV-1 Pol protein as shown in SEQ ID NO:6.

EXAMPLE 20

MRKAd5Nef Construction and Virus Rescue

35 *Construction of vector: shuttle plasmid and pre-adenovirus plasmid* - Key steps performed in the construction of the vectors, including the pre-adenovirus

plasmid denoted MRKAd5nef, is depicted in Figure 23. Briefly, as shown in

Example 19 above, the vector

MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHPA(str.) is the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. It has been modified to

5 contain the *Pac1* site, extension to the packaging signal region, and extension to the pIX gene. It contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*11 site will ensure the direction of transcription of the transgene will be Ad5 E1
10 parallel when inserted into the MRKpAd5(E1-/E3+)Cla1 pre-plasmid. The synthetic full-length codon-optimized HIV-1 nef gene was isolated directly from the plasmid pV1Jns/nef (G2A,LLAA). Digestion of this plasmid with *Bgl*11 releases the pol gene intact, which comprises the nucleotide sequence as disclosed in SEQ ID NO:13. The nef fragment was gel purified and ligated into the

15 MRKpdeIE1+CMVmin+BGHPA(str.) shuttle vector at the *Bgl*11 site. The clones were checked for correction orientation of the gene by using restriction enzyme *Sca*1. A positive clone was isolated and named MRKpdeIE1hCMVminFL-nefBGHPA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows. Shuttle
20 plasmid MRKpdeIE1hCMVminFL-nefBGHPA(s) was digested with restriction enzymes *Pac*1 and *Bst*1107 I (or its isoschizomer, *Bst*Z107 I) and then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla*1 digested) adenoviral backbone plasmid, MRKpAd(E1/E3+)Cla1. The resulting pre-plasmid originally named MRKpdeIE1hCMVminFL-nefBGHPA(s) is now referred to as "pMRKAd5nef". The
25 genetic structure of the resulting pMRKAd5nef was verified by PCR, restriction enzyme and DNA sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the nef transgene in transient transfection cell culture. The complete nucleotide sequence
30 of this pMRKAd5HIV-1nef adenoviral vector is shown in Figure 27A-AM.

Generation of research-grade recombinant adenovirus - The pre-adenovirus plasmid, pMRKAd5nef, was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAdnef was digested with restriction enzyme *Pac*1 (New England Biolabs) and 3.3 µg was
35 transfected per 6 cm dish of PER.C6[®] cells using the calcium phosphate co-precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech

Inc.). *PacI* digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested 6 -10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at $\leq -60^{\circ}\text{C}$. This nef containing recombinant adenovirus is now referred to as "MRKAd5nef".

EXAMPLE 21

Construction of Murine CMV Promoter Containing Shuttle Vectors for Inactivated Pol and Nef/G2A,LLAA

10 The murine CMV (mCMV) was amplified from the plasmid pMH4 (supplied by Frank Graham, McMaster University) using the primer set: mCMV (*Not I*) Forward: 5'-ATA AGA ATG CGG CCG CCA TAT ACT GAG TCA TTA GG-3' (SEQ ID NO: 20); mCMV (*Bgl II*) Reverse: 5'-AAG GAA GAT CTA CCG ACG CTG GTC GCG CCT C-3' (SEQ ID NO:21). The underlined nucleotides represent
15 the *Not I* and the *Bgl II* sites respectively for each primer. This PCR amplicon was used for the construction of the mCMV shuttle vector containing the transgene in the E1 parallel orientation. The hCMV promoter was removed from the original shuttle vector (containing the hCMV-gag-bGHpA transgene in the E1 parallel orientation) by digestion with *Not I* and *Bgl II*. The mCMV promoter (*Not I/Bgl II* digested PCR
20 product) was inserted into the shuttle vector in a directional manner. The shuttle vector was then digested with *Bgl II* and the gag reporter gene (*Bgl II* fragment) was re-inserted back into the shuttle vector. Several clones were screened for correct orientation of the reporter gene. For the construction of the mCMV-gag in the E1 antiparallel orientation, the mCMV promoter was amplified from the plasmid pMH4
25 using the following primer set: mCMV (*Asc I*) Forward: 5'- ATA AGA ATG GCG CGC CAT ATA CTG AGT CAT TAG G (SEQ ID NO:22); mCMV (*Bgl II*) Reverse: 5' AAG GAA GAT CTA CCG ACG CTG GTC GCG CCT C (SEQ ID NO:23). The underlined nucleotides represent the *Asc I* and *Bgl II* sites, respectively for each primer. The shuttle vector containing the hCMV-gag transgene in the E1 antiparallel
30 orientation was digested with *Asc I* and *Bgl II* to remove the hCMV-gag portion of the transgene. The mCMV promoter (*Asc I/Bgl II* digested PCR product) was inserted into the shuttle vector in a directional manner. The vector was then digested with *Bgl II* and the gag reporter gene (*Bgl II* fragment) was re-inserted. Several clones were screened for correct orientation of the reporter gene. For each of the full length
35 IA pol and full length nef/G2A,LLAA genes, cloning was performed using the unique

Bgl II site within the mCMV-bGHpA shuttle vector. The pol and nef genes were excised from their respective pV1Jns plasmids by *Bgl* II digestion.

EXAMPLE 22

5 Construction of mCMV Full Length Inactivated Pol and Full Length nef/G2A.LLAA Adenovectors

Each of these transgenes of Example 21 were inserted into the modified shuttle vector in both the E1 parallel and E1 anti-parallel orientations. *Pac*I and *Bst*Z110I digestion of each shuttle vector was performed and each specific transgene
10 fragment containing the flanking Ad5 sequences was isolated and co-transformed with *Cla* I digested MRKpAd5(E3+) or MRKpAd5(E3-) adenovector plasmids via bacterial homologous recombination in BJ5183 *E. coli* cells. Recombinant pre-plasmid adenovectors containing the various transgenes in both the E3- and E3+ versions (and in the E1 parallel and E1 antiparallel orientations) were subsequently
15 prepared in large scale following transformation into XL-1 Blue *E. coli* cells and analyzed by restriction analysis and sequencing.

EXAMPLE 23

Construction of hCMV-tpa-nef (LLAA) Adenovector

20 The tpa-nef gene was amplified out from GMP grade pV1Jns-tpanef (LLAA) vector using the primer sets: Tpanef (BamHI) F 5'-ATT GGA TCC ATG GAT GCA ATG AAG AGA GGG (SEQ ID 24); Tpanef (BamHI) R 5'-ATA GGA TCC TTA GCA GTC CTT GTA GTA CTC G (SEQ ID NO:25). The resulting PCR product was digested with *Bam*HI, gel purified and cloned into the *Bgl* II site of MRKAd5CMV-bGHpA shuttle vector (*Bgl* II digested and calf intestinal phosphatase treated).
25 Clones containing the tpanef (LLAA) gene (see SEQ ID NO:15 for complet coding region) in the correct orientation with respect to the hCMV promoter were selected following *Sca* I digestion. The resulting MRKAd5tpanef shuttle vector was digested with *Pac* I and *Bst* Z1101 and cloned into the E3+ MRKAd5 adenovector via bacterial
30 homologous recombination techniques.

EXAMPLE 24

Immunogenicity of MRKAd5pol and MRKAd5nef Vaccine

Materials and Methods - Rodent Immunization - Groups of N=10 BALB/c
35 mice were immunized i.m. with the following vectors: (1) MRKAd5hCMV-IApol (E3+) at either 10⁷ vp and 10⁹ vp; and (2) MRKAd5hCMV-IApol (E3-) at either

10⁷ vp and 10⁹ vp. At 7 weeks post dose, 5 of the 10 mice per cohort were boosted with the same vector and dose they initially received. At 3 weeks post the second dose, sera and spleens were collected from all the animals for RT ELISA and IFN γ ELISpot analyses, respectively. For all rodent immunizations, the Ad5 vectors were
 5 diluted in 5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM MgCl₂, 0.005% polysorbate 80, pH 8.0. The total dose was injected to both quadricep muscles in 50 μ L aliquots using a 0.3-mL insulin syringe with 28-1/2G needles (Becton-Dickinson, Franklin Lakes, NJ).

Groups of N=10 C57/BL6 mice were immunized i.m. with the following
 10 vectors: (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+) at either 10⁷ vp and 10⁹ vp; (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10⁷ vp and 10⁹ vp; and (3) MRKAd5mCMV-tpanef(LLAA) (E3+) at either 10⁷ vp and 10⁹ vp. At 7 weeks post dose, 5 of the 10 mice per cohort were boosted with the same vector and dose they initially received. At 3 weeks post the second dose, sera and spleens were
 15 collected from all the animals for RT ELISA and IFN γ ELISpot analyses, respectively.

Non-human Primate immunization - Cohorts of 3 rhesus macaques (2-3 kg) were vaccinated with the following Ad vectors: (1) MRKAd5hCMV-IAPol (E3+) at either 10⁹ vp and 10¹¹ vp dose; and (2) MRKAd5hCMV-IAPol (E3-) at either
 20 10⁹ vp and 10¹¹ vp; (3) MRKAd5hCMV-nef(G2A,LLAA) (E3+) at either 10⁹ vp and 10¹¹ vp; and (4) MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10⁹ vp and 10¹¹ vp. The vaccine was administered to chemically restrained monkeys (10 mg/kg ketamine) by needle injection of two 0.5 mL aliquots of the Ad vectors (in 5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM MgCl₂, 0.005% polysorbate 80, pH 8.0)
 25 into both deltoid muscles. The animals were immunized twice at a 4 week interval (T=0, 4 weeks).

Murine anti-RT and anti-nef ELISA - Anti-RT titers were obtained following standard secondary antibody-based ELISA. Maxisorp plates (NUNC, Rochester, NY) were coated by overnight incubation with 100 μ L of 1 μ g /mL HIV-1 RT protein
 30 (Advanced Biotechnologies, Columbia, MD) in PBS. For anti-nef ELISA, 100 μ L of 1 μ g/mL HIV-1 nef (Advanced Biotechnologies, Columbia, MD) was used to coat the plates. The plates were washed with PBS/0.05% Tween 20 using Titertek MAP instrument (Huntsville, AL) and incubated for 2 h with 200 μ L/well of blocking solution (PBS/0.05% tween/1% BSA). An initial serum dilution of 100-fold was
 35 performed followed by 4-fold serial dilution. 100- μ L aliquots of serially diluted samples were added per well and incubated for 2 h at room temperature. The plates

were washed and 100 μ L of 1/1000-diluted HRP-rabbit anti-mouse IgG (ZYMED, San Francisco, CA) were added with 1 h incubation. The plates were washed thoroughly and soaked with 100 μ L 1,2-phenylenediamine dihydrochloride/hydrogen peroxide (DAKO, Norway) solution for 15 min. The reaction was quenched by adding 100 μ L of 0.5M H₂SO₄ per well. OD₄₉₂ readings were recorded using Titertek Multiskan MCC/340 with S20 stacker. Endpoint titers were defined as the highest serum dilution that resulted in an absorbance value of greater than or equal to 0.1 OD₄₉₂ (2.5 times the background value).

Non-human primate and murine ELISpot assays - The enzyme-linked immuno-spot (ELISpot) assay was utilized to enumerate antigen-specific INF γ -secreting cells from mouse spleens (Miyahira, et al.1995, *J. Immunol. Methods* 181:45-54) or macaque PBMCs. Mouse spleens were pooled from 5 mice/cohort and single cell suspensions were prepared at 5x10⁶/mL in complete RPMI media (RPMI1640, 10% FBS, 2mM L-glutamine, 100U/mL Penicillin, 100 u/mL streptomycin, 10 mM Hepes, 50 uM β -ME). Rhesus PBMCs were prepared from 8-15 mL of heparinized blood following standard Ficoll gradient separation (Coligan, et al, 1998, *Current Protocols in Immunology*. John Wiley & Sons, Inc.). Multiscreen opaque plates (Millipore, France) were coated with 100 μ L/well of either 5 μ g/mL purified rat anti-mouse IFN- γ IgG1, clone R4-6A2 (Pharmingen, San Diego, CA), or 15 μ g/mL mouse anti-human IFN- γ IgG_{2a} (Cat. No. 1598-00, R&D Systems, Minneapolis, MN) in PBS at 4°C overnight for murine or monkey assays, respectively. The plates were washed with PBS/penicillin/streptomycin and blocked with 200 μ L/well of complete RPMI media for 37 °C for at least 2 h.

To each well, 50 μ L of cell samples (4-5x10⁵ cells per well) and 50 μ L of the antigen solution were added. To the control well, 50 μ L of the media containing DMSO were added; for specific responses, either selected peptides or peptide pools (4 μ g/mL per peptide final concentration) were added. For BALB/c mice immunized with the pol constructs, stimulation was conducted using a pool of CD4⁺-epitope containing 20-mer peptides (aa21-40, aa411-430, aa641-660, aa731-750, aa771-790) or a pool of CD8⁺-epitope containing peptides (aa201-220, aa311-330, aa781-800). For C57/BL6 mice immunized with the nef construct, either aa51-70 (CD8⁺ T cell epitope) or aa81-100 (CD4⁺) peptide derived from the nef sequence was added for specific stimulation. In monkeys, the responses against pol were evaluated using two pools (L and R) of 20-aa peptides that encompass the entire pol sequence and overlap by 10 amino acids. In monkeys vaccinated with the nef constructs, a single pool containing 20-mer peptides covering the entire HIV-1 nef sequence and overlapping

by 10 aa was used. Each sample/antigen mixture was performed in triplicate wells for murine samples or in duplicate wells for rhesus PBMCs. Plates were incubated at 37°C, 5% CO₂, 90% humidity for 20-24 h. The plates were washed with PBS/0.05% Tween 20 and incubated with 100 µL/well of either 1.25 µg/mL biotin-conjugated rat anti-mouse IFN-γ mAb, clone XMG1.2 (Pharmingen) or of 0.1 µg/mL biotinylated anti-human IFN-gamma goat polyclonal antibody (R&D Systems) at 4°C overnight. The plates were washed and incubated with 100 µL/well 1/2500 dilution of streptavidin-alkaline phosphatase conjugate (Pharmingen) in PBS/0.005% Tween/5% FBS for 30 min at 37 °C. Spots were developed by incubating with 100 µL/well 1-step NBT/BCIP (Pierce Chemicals) for 6-10 min. The plates were washed with water and allowed to air dry. The number of spots in each well was determined using a dissecting microscope and the data normalized to 10⁶ cell input.

Non-human Primate anti-RT ELISA - The pol-specific antibodies in the monkeys were measured in a competitive RT EIA assay, wherein sample activity is determined by the ability to block RT antigen from binding to coating antibody on the plate well. Briefly, Maxisorp plates were coated with saturating amounts of pol positive human serum (#97111234). 250 uL of each sample is incubated with 15 uL of 266 ng/mL RT recombinant protein (in RCM 563, 1% BSA, 0.1% tween, 0.1% NaN₃) and 20 uL of lysis buffer (Coulter p24 antigen assay kit) for 15 min at room temperature. Similar mixtures are prepared using serially diluted samples of a standard and a negative control which defines maximum RT binding. 200 uL/well of each sample and standard were added to the washed plate and the plate incubated 16-24 h at room temperature. Bound RT is quantified following the procedures described in Coulter p24 assay kit and reported in milliMerck units per mL arbitrarily defined by the chosen standard.

Results - Rodent Studies - BALB/c mice (n=5 mice/cohort) were immunized once or twice with varying doses of MRKAd5hCMV-IApol(E3+) and MRKAd5hCMV-IApol(E3-). At 3 weeks after the second dose, Anti-pol IgG levels were determined by an ELISA assay using RT as a surrogate antigen. Cellular response were quantified via IFNγ ELISpot assay against pools of pol-epitope containing peptides. The results of these assays are summarized in Table 10. The results indicate that the mouse vaccinees exhibited detectable anti-RT IgGs with an adenovector dose as low as 10⁷ vp. The humoral responses are highly dose-dependent and are boostable with a second immunization. One or two doses of either pol vectors elicit high frequencies of antigen-specific CD4⁺ and CD8⁺ T cells; the responses are weakly dose-dependent but are boostable with a second immunization.

Table 10. Immunogenicity of MRKAd5pol Vectors in BALB/c mice.

Group	Vaccine	Dose	No. of Doses	Anti-RT IgG Titers ^a			SFC/10 ⁶ cells ^b		
				GMT	+SE	-SE	Medium	CD4+ peptide pool	CD8+ peptide pool
1	MRKAd5hCMVFLpol (E3+)	10 ⁷ vp	2 1	310419 919	301785 372	163020 265	1(1) 1(1)	75(4) 72(9)	2313(87) 533(41)
2	MRKAd5hCMVFLpol (E3+)	10 ⁹ vp	2 1	1638400 ^b 713155	0 528520	0 303555	2(2) 1(1)	114(9) 48(7)	2083(182) 733(89)
3	MRKAd5hCMVFLpol (E3-)	10 ⁷ vp	2 1	310419 6400	386218 14013	172097 4393	0(0) 10(8)	223(7) 141(21)	2607(27) 409(28)
4	MRKAd5hCMVFLpol (E3-)	10 ⁹ vp	2 1	1638400 ^b 1241675 ^b	0 396725	0 300661	1(1) 0(0)	160(13) 39(13)	2385(11) 833(83)
5	Naïve	none	none	57	9	7	9(2)	11(4)	10(1)

^aGMT, geometric mean titer of the cohort of 5 mice; SE, standard error of the geometric mean^bNear or at the upper limit of the serial dilution; hence, could be greater than this value^cNo. of Spot-forming Cells per million splenocytes; mean values of triplicates are reported along with standard errors in parenthesis.

- 5 C57/BL6 mice were immunized once or twice with varying doses of MRKAd5hCMV-nef(G2A,LLAA) (E3+), MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10⁷ vp and (3) MRKAd5mCMV-tpanef(LLAA) (E3+) at either 10⁷ vp and 10⁹ vp. The immune response were analyzed using similar protocols and the results - listed in Table 11. While anti-nef IgG responses could not be detected in this model system with any of the constructs, there are strong indications of a cellular immunity generated against nef using the ELISpot assay.
- 10

Table 11. Immunogenicity of MRKAd5nef Vectors in C57/BL6 mice.

Group	Vaccine	Dose	No. of Doses	Anti-nef IgG Titers ^a			SFC/10 ⁶ cells ^b		
				GMT	+SE	-SE	Medium	aa51-70 CD8+	aa81-100 CD4+
1	MRKAd5hCMVFLnef (E3+)	10 ⁷ vp	2 1	174 132	70 42	50 32	1(1) 0(0)	23(1) 0(0)	1(1) 0(0)
2	MRKAd5hCMVFLnef (E3+)	10 ⁹ vp	2 1	174 132	70 42	50 32	0(0) 1(1)	61(7) 62(7)	4(2) 3(1)
3	MRKAd5mCMVFLnef (E3+)	10 ⁷ vp	2 1	132 115	42 46	32 33	3(1) 3(2)	15(5) 3(2)	5(2) 4(2)
4	MRKAd5mCMVFLnef (E3+)	10 ⁹ vp	2 1	132 132	42 42	32 32	4(2) 2(1)	83(13) 29(2)	5(1) 4(0)
5	MRKAd5mCMVtpanef(E3+)	10 ⁷ vp	2 1	132 100	42 0	32 0	3(2) 3(1)	14(2) 13(4)	5(1) 10(3)
6	MRKAd5mCMVtpanef(E3+)	10 ⁹ vp	2 1	230 115	170 46	98 33	3(2) 7(1)	145(29) 151(14)	4(0) 10(0)
7	Naïve	none	none	152	78	52	21(2)	18(6)	26(3)

^aGMT, geometric mean titer of the cohort of 5 mice; SE, standard error of the geometric mean^bNo. of spot-forming cells per million splenocytes; mean values of triplicates are reported along with standard errors in parenthesis.

15

Monkey Studies - Cohorts of 3 rhesus macaques were immunized with 2 doses of MRKAd5hCMV-IAPol(E3+) and MRKAd5hCMV-IAPol(E3-). The number of antigen-specific T cells (per million PBMCs) were enumerated using one of two

- peptide pools (L and R) that cover the entire pol sequence; the results are listed in Table 12. Moderate-to-strong T cell responses were detected in the vaccinees using either constructs even at a low dose of 10^9 vp. Longitudinal analyses of the anti-RT antibody titers in the animals suggest that the pol transgene product is expressed efficiently to elicit a humoral response (Table 13). It would appear that generally higher immune responses were observed in animals that received the E3- construct compared to the E3+ virus.

Table 12. Pol-specific T Cell Responses in MRKAd5pol Immunized Rhesus Macaques.

Vaccine (T=0,4 wks)	Monk #	Prebleed			T=4			T=7			T=16		
		Mock	Pol L	Pol R	Mock	Pol L	Pol R	Mock	Pol L	Pol R	Mock	Pol L	Pol R
MRKAd5hCMV-IAPol(E3+) 10^{11} vp	99C100	1	0	0	1	38	31	0	52	148	0	49	715
	99C215	1	2	2	10	98	249	1	109	305	22	88	250
	99D201	5	5	4	6	149	85	0	40	35	0	35	18
MRKAd5hCMV-IAPol(E3+) 10^9 vp	99D212	0	2	0	4	331	114	0	58	14	0	6	6
	99D180	0	4	2	0	19	192	4	36	156	5	38	108
	99C201	8	5	21	6	62	62	0	18	32	1	14	65
MRKAd5hCMV-IAPol(E3-) 10^{11} vp	99D239	5	2	2	20	82	172	1	66	114	9	21	40
	99C186	4	12	6	5	120	421	2	271	489	16	875	530
	99C084	1	8	9	8	84	464	0	14	236	1	24	264
MRKAd5hCMV-IAPol(E3-) 10^9 vp	CC7C	10	10	8	12	724	745	4	322	378	4	188	176
	CD1G	2	0	1	5	474	468	0	232	212	0	101	121
	CD11	6	6	12	10	98	110	5	60	80	8	25	34
Ndve	083Q	nd	nd	nd	nd	nd	nd	4	2	2	2	1	2

nd, not determined

Reported are SFC per million PBMCs; mean of duplicate wells.

Table 13. Anti-RT Ig Levels in MRKAd5pol Immunized macaques.

RT ANTIBODY ASSAY TITERS IN mMU/mL				
Vaccine/Monkey Tag	T=4	T=7	T=12	T=16
MRKAd5hCMV-IAPol(E3+), 10^{11} vp				
99C100	61	1999	5928	4768
99C215	81	1541	2356	2767
99D201	53	336	539	387
MRKAd5hCMV-IAPol(E3+), 10^9 vp				
99D212	10	40	49	68
99D180	<10	36	79	93
99C201	<10	37	71	76
MRKAd5hCMV-IAPol(E3-), 10^{11} vp				
99D239	44	460	1234	1015
99C186	21	233	480	345
99C084	235	2637	2858	1626
MRKAd5hCMV-IAPol(E3-), 10^9 vp				
CC7C	32	175	306	235
CD1G	20	140	273	419
CD11	15	112	149	237

When rhesus macaques were immunized i.m. with two doses of MRKAd5nef

- 5 constructs, vigorous T cell responses ranging from 100 to as high as 1100 per million were observed in 8 of 12 vaccinees (Table 14). The efficacies of the mCMV- and hCMV- driven nef constructs are comparable on the basis of the data generated thus far.

10 Table 14. Nef-specific T cell Responses in MRKAd5nef Immunized Rhesus Macaques.

Vaccine (T=0,4 wks)	Monk #	Pre		T=4		T=7		T=16	
		Mock	Nef	Mock	Nef	Mock	Nef	Mock	Nef
MRKAd5hCMV-nef(G2A,LLAA) (E3+) 10 ¹¹ vp	CD2D	0	4	31	440	4	368	1	251
	CC7B	0	0	2	521	0	178	1	1522
	CC61	2	9	31	112	0	108	11	100
MRKAd5hCMV-nef(G2A,LLAA) (E3+) 10 ⁹ vp	CC2K	9	9	6	52	0	35	0	15
	CD15	5	4	30	998	2	586	0	434
	CD16	6	1	6	1146	0	369	1	212
MRKAd5mCMV-nef(G2A,LLAA) (E3+) 10 ¹¹ vp	99D191	1	5	4	614	0	298	2	419
	99D144	4	6	5	434	0	1100	2	932
	99C193	1	2	1	58	1	22	0	84
MRKAd5mCMV-nef(G2A,LLAA) (E3+) 10 ⁹ vp	99D224	1	11	14	231	1	125	0	70
	99D250	8	9	4	108	0	54	0	5
	99C120	1	6	20	299	0	92	0	79
Naïve	083Q	nd	nd	18	22	4	5	2	1

EXAMPLE 25

- 15 Comparison of Clade B vs. Clade C T Cell Responses in HIV-Infected Subjects

PBMC samples collected from two dozens of patients infected with HIV-1 in US were tested in ELISPOT assays with peptide pools of 20-mer peptides overlapping by 10 amino acids. Four different peptide pools were tested for cross-clade recognition, and they were either derived from a clade B-based isolate (gag H-b; nef-
 20 b) or a clade C-based isolate (gag H-c, nef-c). Data in Table 15 shows that T cells from these patients presumably infected with clade B HIV-1 could recognize clade C gag and nef antigens in ELISPOT assay. Correlation analysis further demonstrated that these T cell responses against clade C gag peptide pool were about 60% of the clade B counterpart (Figure 24), while the T cell responses against clade C nef were
 25 about 85% of the clade B counterpart (Figure 25). These results suggest that cellular immune responses generated in patients infected with clade B HIV-1 can recognize gag and nef antigens derived from clade C HIV-1. These data show that a HIV vaccine, such as a DNA or MRKAd5-based adenoviral vaccine expressing a clade B

gag and/or nef antigen will potentially have the ability to provide a prophylactic and/or therapeutic advantage on a global scale.

5

Table 15
Responses Shown as the Number of gIFN-Secreting T Cells per Million PBMCs

subject	bleed date	gag epitope # (from mapping)	mock	gag H-b	gagH-c	nef-b	nef-c
#100	19-Jul-99	12	10	3950	1385	1295	1300
#101	25-Jul-99	3	15	3885	1280	na	1020
#102	25-Jul-99	4	15	1740	850	1255	1785
#104	7-Jun-99	2	5	1355	1185	na	1060
#107	11-Oct-99	2	25	3305	2795	670	870
#405	11-Jul-99	2	15	4575	3180	1700	1500
#501	19-Jul-99	2	15	1100	570	3365	3460
#505	18-Jul-99	5	10	2145	1725	1235	na
#506	28-Feb-99	2	25	150	45	400	610
#701	28-Mar-99	5	30	7620	4775	3320	2780
#709	17-May-99	3	15	2785	1945	1090	1630
#710	24-May-99	4	5	1055	1080	2210	2140

10

EXAMPLE 26

Characterization and Production of MRKAd5pol and MRKAd5nef
Vectors in Roller Bottles

Expansion of nef and pol Adenovectors - Nef and pol CsCl purified MRKAd5 seeds were used to infect roller bottles to produce P4 virus to be used as a seed for further experiments. P4 MRKAd5 pol and nef vectors were used to infect roller bottles at an MOI 280 vp/cell, except for hCMV-tpa-nef [E3+] which was infected at an MOI of 125 due to low titers of seed obtained at P4.

20

Table 16 Viral particle concentrations for P5 nef and pol adenovectors

Adenovector	AEX Titer (10 ¹⁰ vp/ml culture)	AEX Titer (10 ⁴ vp/cell)	Amplification Ratio
hCMV-FL-nef [E3+]	1.1	0.9	30
mCMV-FL-nef [E3+]	2.2	2.1	75
hCMV-tpa-nef [E3+]	0.07	0.1	5
mCMV-tpa-nef [E3+]	1.3	0.9	35
hCMV-FL-pol [E3+]	2.7	2.1	75
hCMV-FL-pol [E3-]	1.9	1.3	45

- 5 *Roller Bottle Passaging* - Passaging of the *pol* and *nef* constructs continued through passage seven. Cell-associated (freeze/thaw lysis) and whole broth (triton-lysis) titers obtained in all passages were very consistent. In general, MRKAd5pol is ca. 70% as productive as MRKAd5gag while MRKAd5nef is ca. 25% as productive as MRKAd5gag. Samples of P7 virus for both constructs were analyzed by V&CB by
- 10 restriction digest analysis and did not show any rearrangements.

Table 17. Passage Six Viral Productivity for MRKAd5pol and MRKAd5nef

		Xviable (10 ⁶ cells/ml), Viability (%)		Cell Passage Number	AEX Titer (Cell Associated) 10 ¹⁰ vp/ml culture	Titer 10 ⁴ vp/cell	Amplification Ratio	Triton Lysis Titer 10 ¹⁰ vp/ml culture
		Infection	Harvest					
hCMV-FL-nef [E3+]	pool	1.22, 85%		62	0.8	0.7	25	1.6
	1		0.99, 62%					
	2		1.10, 72%					
hCMV-FL-pol [E3+]	pool	1.42, 89%		62	4.5	3.2	115	7.0
	1		1.22, 70%					
	2		1.42, 74%					

15 Table 18. Passage Seven Viral Productivity for MRKAd5pol and MRKAd5nef

		Xviable (10 ⁶ cells/ml), Viability (%)		Cell Passage Number	AEX Titer (Cell Associated) 10 ¹⁰ vp/ml culture	Titer 10 ⁴ vp/cell	Amplification Ratio	Triton Lysis Titer 10 ¹⁰ vp/ml culture
		Infection	Harvest					
hCMV-FL-nef [E3+]	Pool	1.33, 90%		66	1.0	0.8	29	2.1
	1		0.96, 70%					
	2		1.18, 73%					
hCMV-FL-pol [E3+]	Pool	0.90*, 90%		56	4.2	4.7	168	6.5
	1		1.18, 88%					
	2		1.04, 80%					

- MRKAd5nef and MRKAd5pol Viral Production Kinetics* - A timecourse experiment was carried out in roller bottles to determine if the viral production kinetics of the MRKAd5pol and MRKAd5nef vectors were similar to those of
- 20 MRKAd5gag. PER.C6[®] cells in roller bottle cultures were infected at an MOI of 280 vp/cells with P5 MRKAd5pol, P5 MRKAd5nef and P7 MRKAd5gag; for each adenovector, two infected bottles were sampled at 24, 36, 48, and 60 hours post infection. In addition, two bottles were left unsampled until 48 hpi when they were harvested under the Phase I process conditions. The anion-exchange HPLC viral
- 25 particle concentrations of the freeze-thaw recovered cell associated virus at the 24, 36,

48, and 60 hpi timepoints are shown in Figure 29A-B. The QPA titers show a similar trend (data not shown).

Comparison of hCMV- and mCMV-FL-nef - As the titers obtained with the MRKAd5nef construct (hCMV-FL-nef) were lower than those obtained with MRKAd5gag or MRKAd5pol, a viral productivity comparison experiment was performed with mCMV-FL-nef. For each of the two adenovectors (hCMV- and mCMV-FL-nef), two roller bottles were infected at an MOI of 280 vp/cell with passage five clarified lysate. The macroscopic and microscopic observations of the four roller bottles were identical at the time of harvest. Analysis of the clarified lysate produced indicated a higher viral particle concentration in the bottles infected with mCMV-FL-nef, as shown in Table 19. It is stipulated that the higher productivity with mCMV promoter driven nef vector is due to lower nef expression levels in PER.C6[®] cells- experiments are underway at V&CB to measure nef expression levels.

Table 19. Passage Six Viral Productivity Comparison of hCMV- and mCMV-FL-nef

		Xv (10 ⁶ cells/ml), Viability (%)		Cell Passage	AEX Titer	Titer	Amplification	Triton Lysis Titer
		Infection	Harvest	Number	10 ¹⁰ vp/ml culture	10 ⁴ vp/cell	Ratio	10 ¹⁰ vp/ml culture
hCMV-FL-nef (MRKAd5nef)	Pool	1.11, 91%		60	1.5	1.4	50	2.8
	1		1.23, 75%					
	2		1.34, 74%					
mCMV-FL-nef	Pool	1.11, 91%		60	2.3	2.1	75	4.6
	1		1.49, 84%					
	2		1.18, 77%					

20

EXAMPLE 27

Characterization and Large Scale Production of MRKAd5nef Virus in Bioreactors

Materials and Methods - The experiment of the present example was run twice under the following conditions: 36.5°C, DO 30%, pH 7.30, 150rpm agitation rate, no sparging, Life Technologies (Gibco, Invitrogen) 293 SFM II (with 6mM L-glutamine), 0.5M NaOH as base for pH control. During the first run (B20010115), two 10L stirred vessel bioreactors were inoculated with PER.C6[®] cells at a concentration of 0.2x10⁶ cells/ml. Cells were grown until they reached a cell concentration of approximately 1x10⁶ cells/ml. The cells were infected with uncloned MRKAd5nef (G2A,LLAA) at a MOI of 280 virus particles (vp)/cell. For the second batch (B20010202), the same procedure as the first run was used, except the cells

- were infected with cloned MRAd5nef. During both runs, the bioreactors were harvested 48 hours post-infection. Samples were taken and virus concentrations were determined from whole broth (with triton lysis), supernatant, and cell pellets (3 X freeze/thaw) with the AEX and QPA assays. Metabolites were measured with BioProfile 250 throughout the process.

Table 20: Experimental Conditions

Temperature	36.5 °C
DO	30%
PH	7.30
Agitation	150 rpm
Sparging	None

Table 21: Virus source used for experiments.

Run	Batch ID	Cloned/Uncloned MRKAd5nef	MOI (vp/cells)
#1	B20010115-1	Uncloned	280
	B20010115-2	Uncloned	280
#2	B20010202-1	Cloned	280
	B20010202-2	Cloned	280

Results - Table 22 and 23 show an the ability to scale up production of MRKAd5nef by growth in a bioreactor.

Table 22: Virus Concentration as measured by the AEX assay

Run	Batch ID	Cloned/Uncloned MRKAd5nef	Virus Concentration @ 48hpi (1x10 ¹³ vp/L)			
			Supernatant	Clarified Lysate	Total	Triton Lysate
#1	B20010115-1	Uncloned	0.72	3.26	3.98	5.76
	B20010115-2	Uncloned	0.38	1.67	2.05	2.46
#2	B20010202-1	Cloned	0.80	6.00	6.80	8.88
	B20010202-2	Cloned	0.50	6.00	6.50	8.47

Table 23: Virus Titers as measured by the QPA assay

Run	Batch ID	Cloned/Uncloned MRKAd5nef	Virus Concentration @ 48hpi (1x10 ¹¹ IU/L)				
			Whole Broth	Supernatant	Clarified Lysate	Total	Triton Lysate
#1	B20010115-1	Uncloned	0.13	1.12	1.76	2.88	11.28
	B20010115-2	Uncloned	0.14	0.73	1.54	2.27	5.86
#2	B20010202-1	Cloned	0.14	0.97	1.62	2.69	11.89
	B20010202-2	Cloned	0.14	1.17	1.70	2.97	12.47

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art

from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

EXAMPLE 28

5 MRKAd5HIV-1gag Boosting of DNA-Primed Animals

Groups of 3-5 rhesus macaques were immunized with (a) 5 mgs of V1Jns-Flgag (pV1JnsCMV(no intron)-FL-gag-bGHpA), (b) 5 mgs of V1Jns-Flgag formulated with 45 mgs of a non-ionic block copolymer CRL1005, or (c) 5 mgs of
10 V1Jns-Flgag formulated with 7.5 mgs of CRL1005 and 0.6 mM benzalkonium chloride at weeks 0, 4, and 8. All animals received a single dose of 10^7 viral particles (vp) of the MRKAd5HIV-1gag at week 26. Note: 10^7 is too low to prime or boost effectively when used as a single modality (dose is selected to mimic preexposure to adenovirus); see Figure 32.

15 Blood samples were collected from all animals at several time points and peripheral blood mononuclear cells (PBMCs) were prepared using standard Ficoll method. The PBMCs were counted and analyzed for gamma-interferon secretion using the ELISpot assay (Table 24). For each monkey, the PBMCs were incubated overnight either in the absence (medium) or presence of a pool (called "gag H") of 50
20 20-aa long peptides that encompass the entire HIV-1 gag sequence.

The results indicate that MRKAd5HIV-1gag was very effective in boosting the T cell immune responses in these monkeys. At week 28 or 2 weeks after the viral boost, the number of gag-specific T cells per million PBMCs increased 2-48 fold compared to the levels observed at week 24 or 2 weeks prior to the boost.

25 The PBMCs were also analyzed by intracellular gamma-interferon staining prior to (at week 10) and after the MRKAd5gag boost (at week 30). The results for select animals are shown on Figure 31. The results indicate that (a) immunization with DNA/adjuvant formulation elicited T cell responses which can either be balanced, $CD4^+$ -biased or $CD8^+$ -biased, and (b) boosting with the MRKAd5gag
30 construct produced in all cases a strongly $CD8^+$ -biased response. These results suggest that boosting with MRKAd5HIV-1gag construct is able to improve the levels of antigen-specific $CD8^+$ T cells.

Table 24. Boosting of DNA/Adjuvant-Primed Rhesus Monkeys with MRKAd5gag

Grp#	Priming T=0, 4, 8 wks DNA/5 mgs PBS (D101)	Boost T=28 wks MRKAd5gag(E3+) 10 ⁷ vp	Munk#	T=0		T=4		T=6		T=10		T=17		T=24		T=28		T=30	
				Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H
1	DNA/5 mgs + CRL1005/5 mgs	MRKAd5gag(E3+) 10 ⁷ vp	CB5H	NA	NA	3	35	15	71	4	224	8	115	8	05	19	556	0	316
			CC6X	0	0	0	15	0	46	0	68	0	76	0	35	3	1705	1	755
			AW3G	5	11	0	35	3	51	3	46	2	89	8	65	10	989	0	355
2	DNA/5 mgs + CRL1005/5 mgs	MRKAd5gag(E3+) 10 ⁷ vp	CC1C	0	4	1	60	0	111	5	270	4	260	8	232	3	959	19	1345
			CC1K	4	0	1	101	0	254	0	781	5	452	0	321	0	1815	1	1099
			AW3P	9	8	1	10	4	71	4	164	8	104	5	85	11	836	6	241
3	DNA/5 mgs + CRL1005/7.5 mgs + 0.6 mM BAK	MRKAd5gag(E3+) 10 ⁷ vp	CB5F	NA	NA	0	31	0	288	0	530	19	374	9	251	8	1549	20	1734
			AK8B	9	12	4	36	1	119	0	439	0	425	0	316	4	1229	5	1354
			AW2D	10	4	1	59	5	264	19	425	6	105	9	205	19	585	8	404
4	none	None	CA4R	1	0	3	121	1	135	1	270	5	130	1	105	14	1384	10	978
			CB58	8	6	0	6	3	119	0	274	6	282	1	208	0	636	1	828
			CB5W	4	3	0	26	1	91	0	139	0	164	1	82	5	543	1	349
			CB7D	1	0	0	136	0	316	1	609	5	625	1	759	0	2278	4	1831
4	none	None	98D201	3	0	0	0	1	0	0	0	0	1	1	2	3	0	0	0

NA, not available

EXAMPLE 29

Construction of gagpol fusion for MRKAd5gagpol fusion constructs

5 The open reading frames for the codon-optimized HIV-1 gag gene was fused directly to the open reading frame of the IA pol gene (consisting of RT, RNaseH and integrase domains) by stepwise PCR. Because the gene (SEQ ID NO: 38) does not include the protease gene and the frameshift sequence, it encodes a single polypeptide of the combined size of p55, RT, RNase H and integrase (1350 amino acids; SEQ ID NO: 39).

10 The fragment that extends from the BstEII site within the gag gene to the last non-stop codon was ligated via PCR to a fragment that extends from the start codon of the IAPol to a unique BamHI site. This fragment was digested with BstEII and BamHI. Construction of gag-IAPol fusion was achieved via three-fragment ligation involving the PstI-BstEII gag digestion fragment, the BstEII/BamHI digested PCR
15 product and long PstI/BamHI V1R-FLpol backbone fragment.

The MRKAd5-gagpol adenovirus vector was constructed using the BglII fragment of the V1R-gagpol containing the entire ORF of gag-IAPol fusion gene.

EXAMPLE 30

20 Immunogenicity Studies in Non-Human Primates

Cohorts of three (3) macaques were immunized with 10e8 or 10e10 viral particles (vp) of one of the following MRKAd5 HIV-1 vaccines: (1) MRKAd5gag; (2) MRKAd5pol; (3) MRKAd5nef; (4) a mixture containing equal amounts of
25 MRKAd5gag, MRKAd5pol, and MRKAd5nef, or (5) a mixture of equal amounts of MRKAd5gagpol and MRKAd5nef. The vaccines were administered at weeks 0 and 4.

The T cell responses against each of the HIV-1 antigens were assayed by IFN-gamma ELISpot assay using pools of 20-aa peptides that encompass the entire protein
30 sequence of each antigen. The results (Table 25) are expressed as the number of spot-forming cells (sfc) per million peripheral blood mononuclear cells (PBMC) that respond to each of the peptide pools.

Results indicate the following observations: (1) each of the single gene constructs (MRKAd5gag, MRKAd5pol, or MRKAd5nef) is able to elicit high levels
35 of antigen-specific T cells in monkeys; (2) the single-gene MRKAd5 constructs can be mixed as a multi-cocktail formulation capable of eliciting very broad T cell responses against gag, pol, and nef; (3) the MRKAd5 vector expressing the fusion

protein of gag plus IA pol is capable of inducing strong T cell responses to both gag and pol.

5 **Table 25. Evaluation of Mixtures of MRKAd5 vectors expressing humanized HIV-1 gag, pol, gagpol, nef in rhesus macaques**

Grp #	Vaccine T=0, 4 wks	Monk #	T=6 wks				
			Mock	Gag H	Pol - 1	Pol - 2	Nef
1	MRKAd5 gag 10 ¹⁰ vp	CB9V	0	15	-	-	-
		CD19	0	374	-	-	-
		109H	1	843	-	-	-
2	MRKAd5 gag 10 ⁸ vp	99D130	1	948	-	-	-
		W277	16	324	-	-	-
		143H	4	595	-	-	-
3	MRKAd5 pol 10 ¹⁰ vp	CC1X	4	-	46	256	-
		AW3W	3	-	463	550	-
		AV43	6	-	95	1333	-
4	MRKAd5 pol 10 ⁸ vp	AW38	1	-	19	30	-
		CC8K	0	-	50	995	-
		CC21	1	-	33	436	-
5	MRKAd5 nef 10 ¹⁰ vp	076Q	9	-	-	-	1204
		091Q	4	-	-	-	85
		083Q	0	-	-	-	176
6	MRKAd5 nef 10 ⁸ vp	00C029	1	-	-	-	114
		98D022	6	-	-	-	170
		98D160	3	-	-	-	198
7	MRKAd5gag+MRKAd5pol+MRKAd5nef 10 ¹⁰ vp each	99D251	3	206	15	193	120
		05H	3	135	21	9	638
		00C016	3	26	4	51	23
8	MRKAd5gag+MRKAd5pol+MRKAd5nef 10 ⁸ vp each	99D215	1	171	18	193	240
		81H	5	73	6	14	243
		12H	8	1140	115	811	719
9	MRKAd5gagpol +MRKAd5 nef 10 ¹⁰ vp each	99D211	0	83	56	838	725
		22H	4	385	119	1194	1915
		61H	4	343	11	765	853
10	MRKAd5gagpol +MRKAd5 nef 10 ⁸ vp each	34H	3	78	19	5	75
		48H	1	65	105	46	43
		70H	5	158	15	220	191

Indicated are numbers of spot-forming cells per million PBMCs against the peptide pools. Mock, no peptides; gag H, fifty 20-aa peptides encompassing p55 sequence; pol-1, 20-aa peptides representing N-terminal half of IA pol; pol-2, 20-aa peptides representing the carboxy-terminal half of IA pol; nef, 20-aa peptides encompassing the entire wild-type nef sequence. Responses to the antigens prior to the first immunization did not exceed 40 sfc/10⁶ PBMC.

WHAT IS CLAIMED IS

1. A recombinant adenoviral vaccine vector at least partially deleted in
5 E1 and devoid of E1 activity, comprising:
- a) an adenovirus *cis*-acting packaging region corresponding to from
about base pair 1 to between from about base pair 400 to about
base pair 458 of a wildtype adenovirus genome; and
 - b) a gene encoding an HIV protein or immunologically relevant
10 modification thereof.
2. A vector in accordance with claim 1 comprising a packaging region
corresponding to from about base pair 1 to about base pair 450 of a wildtype
adenovirus genome.
3. A vector in accordance with claim 1 further comprising nucleotides
15 corresponding to between from about base pair 3511 to about 3524 to about base pair
5798 of a wildtype adenovirus genome.
4. A vector in accordance with claim 3 comprising base pairs
corresponding to 1-450 and 3511-5798 of a wildtype adenovirus genome.
5. A vector in accordance with claim 4 which is deleted of base pairs
20 451-3510.
6. A vector in accordance with claim 1 which is at least partially
deleted in E3.
7. A vector in accordance with claim 6 wherein the E3 deleted region
is from base pairs 28,133-30,818.

8. A vector in accordance with claim 1 wherein the gene encoding the HIV protein or modification thereof comprises codons optimized for expression in a human.

9. A vector in accordance with claim 1 wherein the vector comprises a
5 gene expression cassette comprising:

a) a nucleic acid encoding a protein;
b) a heterologous promoter operatively linked to the nucleic acid
encoding the protein; and

(c) a transcription termination sequence.

10 10. A vector in accordance with claim 9 wherein the gene expression cassette is inserted into the E1 region.

11. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette is in an E1 parallel orientation

12. An adenoviral vector in accordance with claim 9 wherein the gene
15 expression cassette is in an E1 antiparallel orientation.

13. An adenoviral vector in accordance with claim 9 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

14. An adenoviral vector in accordance with claim 13 wherein the promoter is an immediate early human cytomegalovirus promoter.

20 15. An adenoviral vector in accordance with claim 9 wherein the promoter is a murine cytomegalovirus promoter.

16. An adenoviral vector in accordance with claim 9 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

17. An adenoviral vector in accordance with claim 9 wherein the transcription termination sequence is a synthetic polyadenylation signal (SPA).

18. A cell comprising the adenoviral vector of claim 1.

19. Recombinant, replication-defective adenovirus particles harvested
5 and purified subsequent to transfection of the adenoviral vector of claim 1 into a cell line which expresses adenovirus E1 protein at complementing levels.

20. An HIV vaccine composition comprising purified adenovirus particles of claim 19.

21. An HIV vaccine composition of claim 20 which comprises a
10 physiologically acceptable carrier.

22. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 1 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant,
15 replication-defective adenovirus.

23. A method according to claim 22 wherein the cell is a PER.C6[®] cell.

24. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of
20 claim 21.

25. A method according to claim 24 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

26. A method according to claim 25 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

27. A method according to claim 24 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

28. A method according to claim 24 which comprises administering and readministering the adenovirus vaccine vector to the individual.

29. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV gag or an immunologically relevant modification thereof.

30. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV gag protein or immunologically relevant modification thereof.

31. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

- a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and
- b) a gene expression cassette comprising
 - i) SEQ ID NO: 29;
 - ii) a heterologous promoter operatively linked to i); and
 - iii) a transcription termination sequence.

32. An adenoviral vector in accordance with claim 31 wherein the gene expression cassette is in an E1 parallel orientation.

33. An adenoviral vector in accordance with claim 31 wherein the gene expression cassette is in an E1 antiparallel orientation.

5 34. An adenoviral vector in accordance with claim 31 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

35. An adenoviral vector in accordance with claim 31 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

10 36. An adenoviral vector in accordance with claim 31 which is at least partially deleted in E3.

37. A cell comprising the adenoviral vector of claim 30.

38. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 30 into a cell
15 line which expresses adenovirus E1 protein at complementing levels.

39. An HIV vaccine composition comprising purified adenovirus particles of claim 38.

40. An HIV vaccine composition of claim 39 which comprises a physiologically acceptable carrier.

20 41. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 30 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

42. A method according to claim 41 wherein the cell is a PER.C6[®] cell.

43. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of
5 claim 21.

44. A method according to claim 43 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

10 45. A method according to claim 44 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

46. A method according to claim 43 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

15 47. A method according to claim 43 which comprises administering and readministering the adenovirus vaccine vector to the individual.

48. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV pol or an immunologically relevant modification thereof.

49. An adenoviral vector in accordance with claim 9 wherein the gene
20 expression cassette comprises an open reading frame encoding an HIV pol protein or immunologically relevant modification thereof.

50. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

- 5 a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and
- b) a gene expression cassette comprising
- i) a nucleotide sequence selected the group consisting of SEQ ID NO: 1, SEQ ID NO: 5 and SEQ ID NO: 7;
 - ii) a heterologous promoter operatively linked to i); and
 - 10 iii) a transcription termination sequence.

51. An adenoviral vector in accordance with claim 50 wherein the gene expression cassette is in an E1 parallel orientation.

52. An adenoviral vector in accordance with claim 50 wherein the gene expression cassette is in an E1 antiparallel orientation.

15 53. An adenoviral vector in accordance with claim 50 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

54. An adenoviral vector in accordance with claim 50 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

20 55. An adenoviral vector in accordance with claim 50 which is at least partially deleted in E3.

56. A cell comprising the adenoviral vector of claim 49.

57. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 49 into a cell line which expresses adenovirus E1 protein at complementing levels.

58. An HIV vaccine composition comprising purified adenovirus
5 particles of claim 57.

59. An HIV vaccine composition of claim 58 which comprises a physiologically acceptable carrier.

60. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of
10 claim 49 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

61. A method according to claim 60 wherein the cell is a PER.C6[®] cell.

15 62. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of claim 59.

63. A method according to claim 62 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with
20 a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

64. A method according to claim 63 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

65. A method according to claim 62 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

66. A method according to claim 62 which comprises administering and readministering the adenovirus vaccine vector to the individual.

5 67. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV nef or an immunologically relevant modification thereof.

68. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV nef protein or immunologically relevant modification thereof.

10 69. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs
15 corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and

b) a gene expression cassette comprising

i) a nucleotide sequence selected the group consisting of
SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13 and
20 SEQ ID NO: 15;

ii) a heterologous promoter operatively linked to i); and

iii) a transcription termination sequence.

70. An adenoviral vector in accordance with claim 69 wherein the gene expression cassette is in an E1 parallel orientation.

71. An adenoviral vector in accordance with claim 69 wherein the gene expression cassette is in an E1 antiparallel orientation.

72. An adenoviral vector in accordance with claim 69 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

5 73. An adenoviral vector in accordance with claim 69 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

74. An adenoviral vector in accordance with claim 69 which is at least partially deleted in E3.

10 75. A cell comprising the adenoviral vector of claim 68.

76. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 68 into a cell line which expresses adenovirus E1 protein at complementing levels.

15 77. An HIV vaccine composition comprising purified adenovirus particles of claim 76.

78. An HIV vaccine composition of claim 77 which comprises a physiologically acceptable carrier.

79. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 68 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

20

80. A method according to claim 79 wherein the cell is a PER.C6[®] cell.

81. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of claim 78.

82. A method according to claim 81 which further comprises
5 administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

83. A method according to claim 82 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus
10 vaccine.

84. A method according to claim 81 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

85. A method according to claim 81 which comprises administering and readministering the adenovirus vaccine vector to the individual.

86. A multivalent adenovirus vaccine composition comprising
15 recombinant, replication-defective adenovirus particles, wherein the adenovirus particles are harvested and purified from a cell line expressing adenovirus E1 protein, and wherein the particles are harvested subsequent to transfection of the cells with an adenoviral vector or vectors in accordance with claim 9; said vector(s) comprising a
20 gene expression cassette or cassettes comprising nucleotide sequences encoding HIV proteins selected from the group consisting of:

- a) gag, pol, and nef, expressed independently from three individual vectors;

- b) gag, pol, and nef, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- c) gag, pol, and nef, expressed via two vectors, one expressing a pol-nef fusion, and another expressing gag;
- d) gag, pol, and nef, expressed via two vectors, one expressing a gag-pol fusion and another expressing nef;
- e) gag, pol and nef, expressed via two vectors, one expressing a nef-gag fusion and another expressing pol;
- f) gag, pol, and nef, expressed via one vector expressing a gag-pol-nef fusion;
- g) gag and pol, expressed independently from two individual vectors;
- h) gag and pol, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- i) pol and nef, expressed independently from two individual vectors;
- j) pol and nef, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- k) nef and gag, expressed independently from two individual vectors;
- l) nef and gag, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- m) gag and pol, expressed via one vector expressing a gag-pol fusion;

n) pol and nef, expressed via one vector expressing a pol-nef fusion;
and

o) nef and gag, expressed via one vector expressing a nef-gag fusion.

87. A multivalent adenovirus vaccine composition in accordance with
5 claim 86 wherein the gag-pol fusion consists of SEQ ID NO: 39.

88. A multivalent adenovirus vaccine composition in accordance with
claim 86 wherein the fused sequences have the encoding nucleic acid sequences
operatively linked to distinct promoters and transcription termination sequences.

89. A multivalent adenovirus vaccine composition in accordance with
10 claim 86 wherein the fused sequences have the encoding nucleic acid sequences
operatively linked to a single promoter; and the encoding nucleic acid sequences
operatively linked by an internal ribosome entry sequence ("IRES").

Original Adenovector Construct:

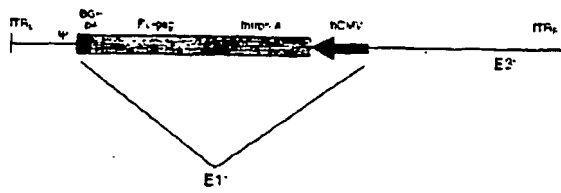


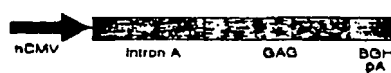
Figure 1: Original HIV-1 gag adenovector.

Sequence of the open reading frame for FL-gag (human codon optimized)

atgggtgctagggcttctgtgctgtctgggtggtagctggacaagtgggagaagatcaggctgaggcctgggtg
caagaagaagtacaagctaaagcacatgtgtggccctccaggagctggagagggttctgtgaacctggc
ctgtggagacctctgaggggtgcaggcagatcctggccagctccagccctccctgcaaacaggctctgagg
agctgaggtccctgtacaacacagtggctacccgtactgtgtgcaccagaagattgatgtgaaggacaccaag
gaggccctggagaagattgaggaggagcagaacaagtccaagaagaaggcccagcaggctgtgtgtggc
acaggcaactccagccagggtgtccagaactacccattgtgcagaacctccaggggccagatgggtgcaccag
ggcatctccccccggacctggaatgctgggtgaagggtggaggagaaggccttctccctgagggtgatccc
catgttctgtccctgtctgaggggtgtccacccccaggacctgaacacattgtgtgaacacagtggggggccatc
aggctgccatgcagatgtgtgaaggagacatcaatgaggaggctgtgtgtgtggacaggctgtcatcctgtgc
acgtgtggccctattgcccccgccagatgaggaggagccaggggtctgtacattgtgtgaccacctccacct
ccaggagcagattggctggatgaccaacaaccccccatcctgtgggggaaatctacaagagggtggatcat
cctgggctgaacaagattgtgaggatgtactccccaccctccatcctggacatcaggcaggggcccaaggag
ccctcaggggactatgtggacagggttctacaagacctgagggtgtgagcaggcctccaggagggtgaagaact
ggatgacagagacctgtgtgtgcagaatgccaaacctgactgcaagaccatcctgaaggccctggggccctg
ctgccacctggaggagatgtgacagcctgcccagggggtggggggccctgggtcacaaggccagggtgtgtg
gtgaggccatgtcccagggtgaccaactccgccacatcatgtgagagggggcaacttcagggaaccagag
gaagacagtgaagtgtctcaactgtggcaagggtgggccacattgccaaagaactgtaggggccccagggaaga
agggtgtgtggaagtgtggcaaggaggggccaccagatgaaggactgcaatgagaggcaggccaacttctg
ggcaaaatctggccctcccaaggggcaggcctggcaacttctccagtcaggcctgagcccacagcccct
cccgaggagtcctcagggttggggaggagaagaccacccccagccagaagcaggagcccatgacaagg
agctgtacccccctggcctccctgagggtccctgtttggcaacgaccttctccaglaaaataaagccgggca
gat (SEQ ID NO: 29)

Figure 2

Old Transgene:



New Transgenes:

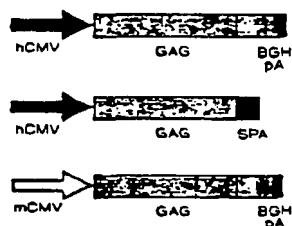


Figure 3: Diagrammatic representation of the original HIV-1 gag transgene and the series of new transgene constructions.

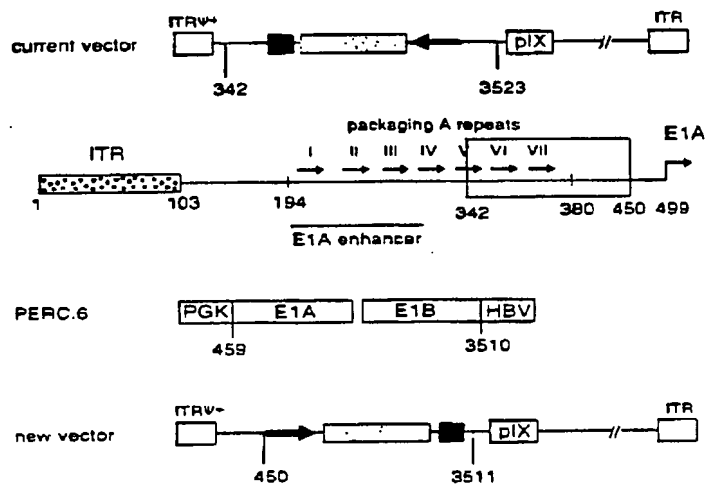


Figure 4: Modifications made to the current adenovector backbone in the generation of the new vector.

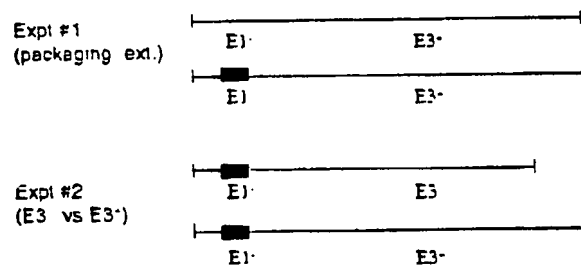


Figure 5: Virus mixing experiments to determine the effects of the addition made to the packaging signal region (Expt #1) and analysis of the effects of the E3 gene on viral growth (Expt. #2). The red bars denote the region of modifications made to the E1 deletion.

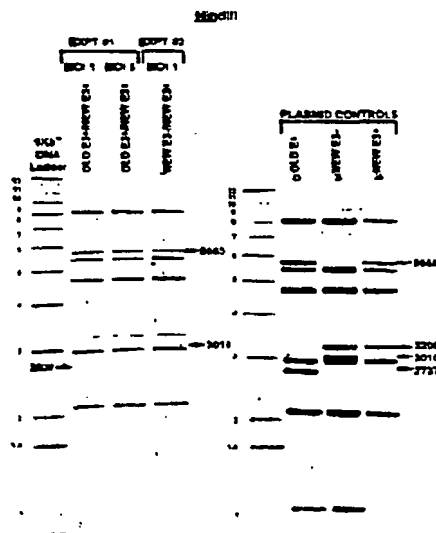


Figure 6: Autoradiograph of viral DNA analysis following viral mixing experiments (expts. #1 and #2) as detailed in the text.

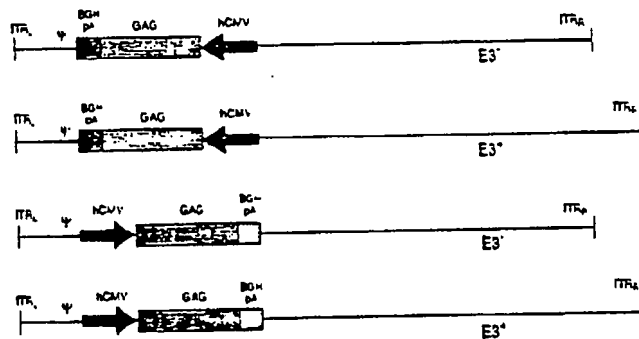


Figure 7A: hCMV-FLgag-bGHpA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3- and E3+ backbones were constructed.

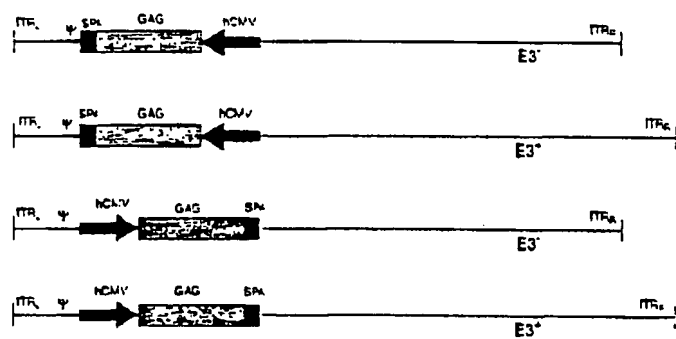


Figure 7B: hCMV-FLgag-SPA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3⁻ and E3⁺ backbones were constructed.

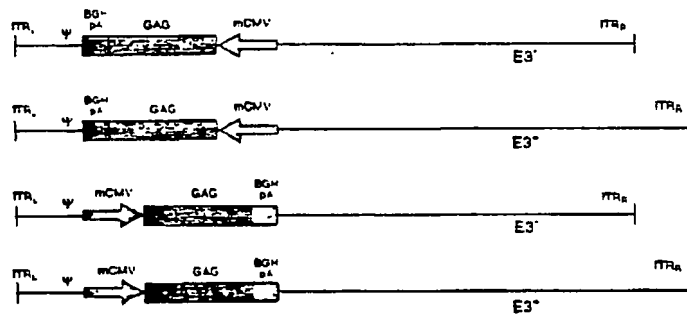


Figure 7C: mCMV-FLgag-bGHpA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3- and E3+ backbones were constructed.

Plasmid mixing expt: (orientation)

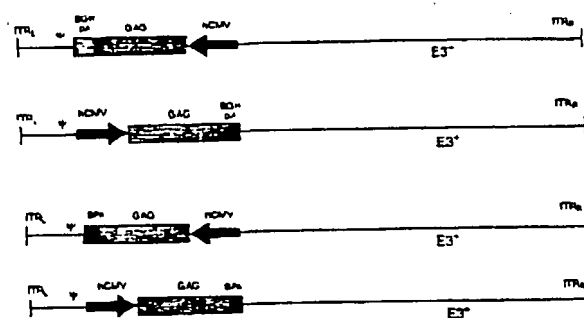


Figure 8A: Effect of transgene orientation

Plasmid Mixing expt: (poly A signal)

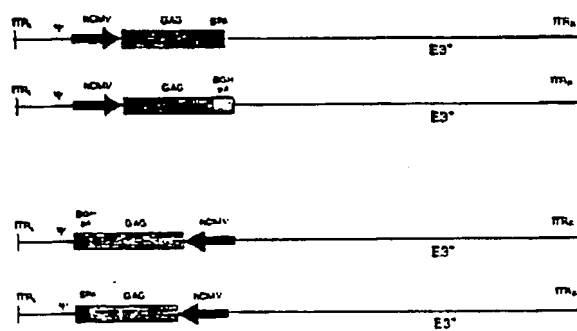


Figure 8B: Effect of polyadenylation signal

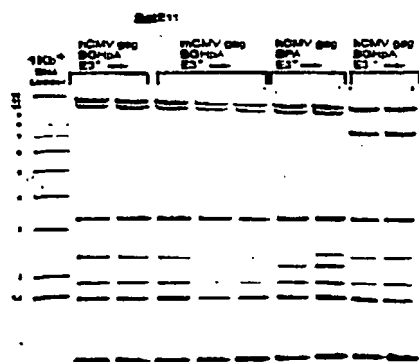


Figure 9: Viral DNA from the four Adgag candidates at P5, following *EcoE11* digestion.

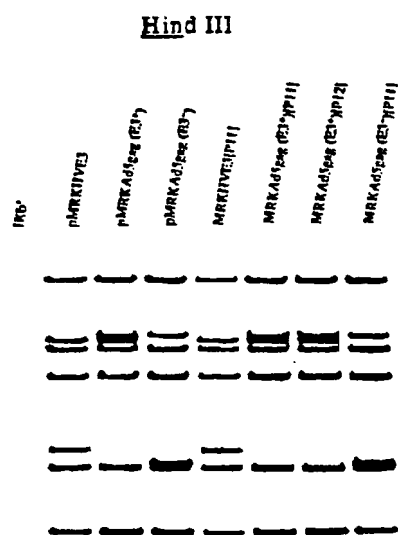


Figure 10: Viral DNA analysis of passage 11 and/or 12 of MRKHVE3, MRKAd5gag and MRKAd5gag(E3-).



Figure 11: Viral DNA analysis (*Hind*III digestion) of passage 6 MRKHVE3 and MRKAd5gag used to initiate the viral competition study. Last two lanes are passage 11 analysis of duplicate passages of the competition study (each virus at MOI 280 vp).

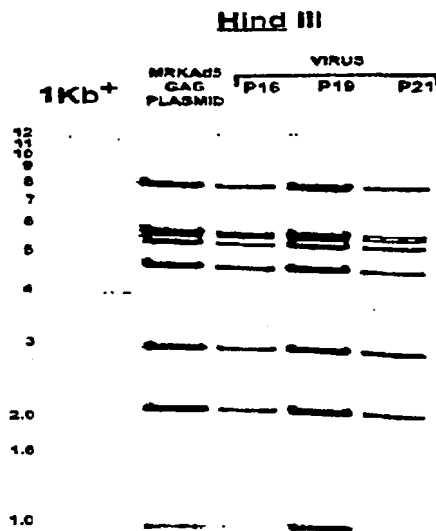
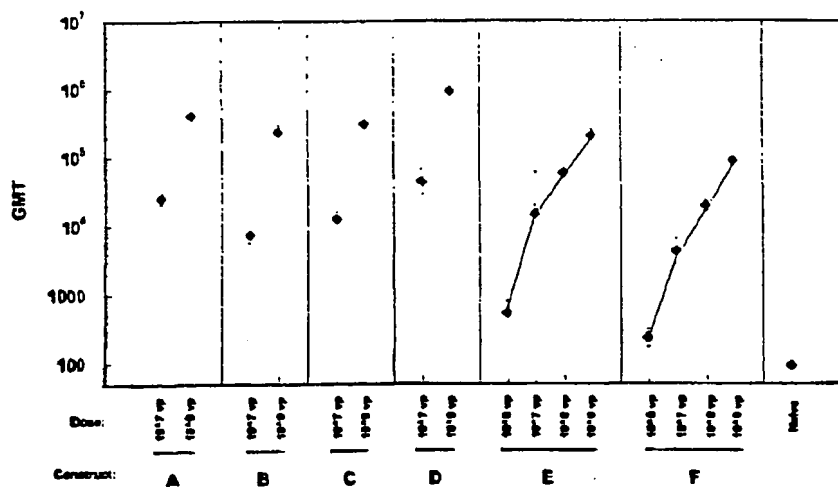


Figure 12: Viral DNA analysis by *Hind*III digestion on high passage numbers for MRKAd5gag in serum containing media with collections made at specified times. The first lane shows the 1 Kb DNA size marker. The other lanes represent pre-plasmid control (digested with Pac1 and *Hind*III), and MRKAd5gag virus continually passaged to P16, P19 and P21 (serum containing media).

13
Figure 13. Serum anti-p24 Levels at 3 Wks post i.m. immunization of balb/c mice (n=10) with Varying Doses of Several Adgag constructs: (A) MRKAd5gag (through passage 5); (B) MRKAd5 E3⁺ hCMV-FLgag-bGHpA; (C) MRKAd5 E3⁺ hCMV-FLgag-SPA; (D) MRKAd5 E3⁺ mCMV-FLgag-bGHpA; (E) research Lot (293 cell-derived) of Ad5HIV-1gag; and (F) clinical lot (Ad5gagFN0001) of Ad5HIV-1gag. Reported are the geometric mean titers (GMT) for each cohort.



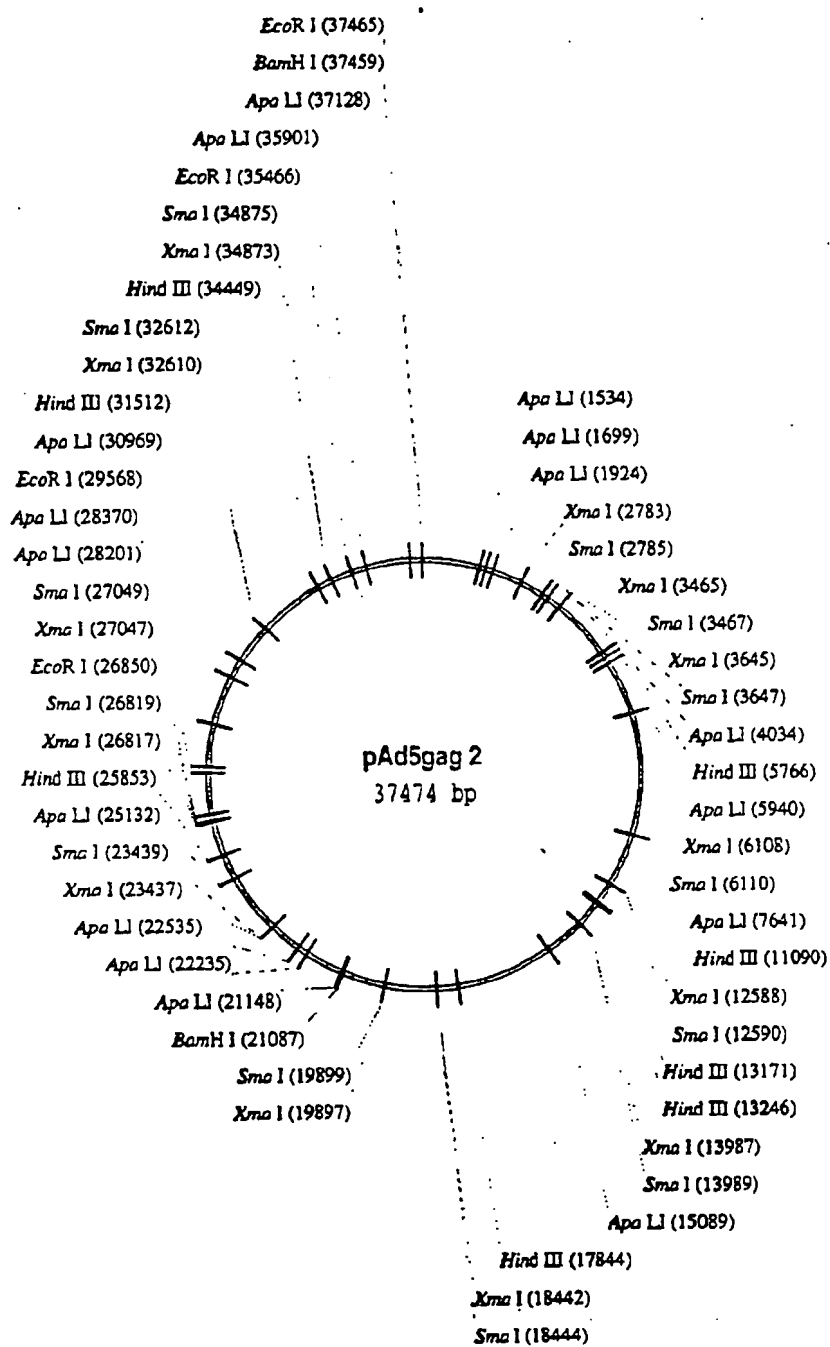


Figure 14

pMRKAd5seq MEM682

1	TTCTTAATTA	ACATCATCAA	TAATATACCT	TATTTGGAT	TGAAATCAAT	ATGATTAATTA	GGTGTGTGAG	TTTGTGACCT	GGGCGGGGCG	GTGGTAACTG
	AGAATTAAT	TCTAGTAGTT	ATTATATACA	ATAAACCTTA	ATTTGATTA	TACTATTACT	CTCCACAGCTC	AAACACTGCA	CCCGCGCCCG	CACCTTTGTA
101	GGGGGTGAC	GTAGTAGTGT	GGCGAATG	TGATATACCA	ACGTATGAG	AGCATATGAT	AGTATGAGT	GTGGCAAAAG	TGACGTTTTT	GTGTATGTT
	CGCGCCACTG	CATCATACA	CGCGTTCCAC	ACTCAACCT	TCATACCCCG	TGATATGAT	TGCTGTGCTA	CACGTTTTTC	ACTGCAAAA	CCACACCGG
201	GGGTATACAA	GGATGTACA	ATTTTGGG	GGTTTATGCG	GGATATGCTA	GTAAATTTG	GTCTAAACCA	GTAAAGATTTG	GCCATTTTGG	GTGCAAAAT
	CCACATGTGT	CGATCAGCT	TAAATGCTG	CCAAATGCG	CCTAACACT	CATTATGAG	CGATATGCT	CATTATTAAC	CGGTAAAGC	GGCTTTTGA
301	GAATAAGAG	AGTGAATC	TGATATATTT	TTGTATCTC	ATATGCTTA	ATATTTGCT	AGTGGCGCG	GGACTTTTAC	CGTTTACGTT	GACACTGAC
	CTTATTTCC	TTTACTTAG	ACTTATTAAA	ACCAATGAG	TATATGCTAT	TATATGCTAT	TATATATTA	GGTGGCGCG	CGTAAACTG	CTCTGAGCG
401	CAGGTGTTTT	TCTCAGGTGT	TTTCCGCTT	CGCGTCAAA	GTATGCTTT	TATATATTA	GGTGGCGCG	ATCCATTTGCA	TACGTTGTAT	CCATATTCAT
	GTCCACAAA	AGATGCCACA	AAATGCTCA	GGCCGAGTTT	CAATGCTAAA	ATATATATTA	CGCGCGCGCG	TAGTAACTG	ATCCAACTTA	GGTATATAT
501	ATATGTACAT	TTATATTGCG	TCATGTCCAA	CATTACCGCG	ATATGCTAT	TGATATTTCA	CTAGTTATTA	ATAGTAACTA	ATTAGCGGCT	CATTATTTCA
	TATACATGTA	AATATATCCG	ACTACAGGTT	GTATATGCTG	TATACGCTA	ACTAATTAAT	GATCAATTAAT	TATCATTAGT	TAAATGCCCCA	GTAAATCAAT
601	TAGCCCATAT	ATGATGTCC	GGTTTACATA	ACTTACGGTA	AAATGCTGCT	CTGTATAC	GGCGTTGCTG	GGCGCGGTA	ACTGCACTA	ATATGAGTAT
	ATCGGTATTA	TACCTCAAGG	CCCATGTAT	TGATATGCT	TTACCGGCG	GACCGACTG	CGGTATGCTG	GGCGCGGTA	ACTGCACTA	TTACTGCATA
701	GTTCCTATAG	TAAAGCCAT	AGGACTTTTC	CATTACCTC	ATATGCTG	TATATTTCT	TAAATTTCC	ACTTGGCGCT	ACATCAAGT	TATCATATTA
	CAAGGTATC	ATTTGCGTTA	TCCCTGAAAG	GTAACTGAG	TTACCGCT	CATTAATTT	ATTTGAGCG	TAAACGCTCA	TGTATTTTAC	ATAGTATATC
801	CAAGTACCGC	CCCTATTTGAC	GTCAATGAG	GTAAATGCG	CGCTGCTG	TATGCTCAT	ATGCTGCTG	ATGCTGCTG	AGTATGCTG	ATATATCTA
	GTTCATGCG	GGATTAACCTG	CATTACTGCG	CATTACTGCG	CGCTGCTG	TATGCTCAT	ATGCTGCTG	ATGCTGCTG	AGTATGCTG	ATATATCTA
901	CGTATATAGC	ATGCTATTA	CCATGCTGAT	CCATGCTGAT	CGCTGCTG	TATGCTCAT	ATGCTGCTG	ATGCTGCTG	AGTATGCTG	ATATATCTA
	GCATATATAG	TAGCATATAT	GGTATGCTAT	GGTATGCTAT	CGCTGCTG	TATGCTCAT	ATGCTGCTG	ATGCTGCTG	AGTATGCTG	ATATATCTA
1001	ATTTGAGCTCA	ATGAGAGTTT	GTTTTGGCAC	CAAAATCAAC	GGGCTTTTGG	CAGTATATCA	ATGCTGCTG	ATGCTGCTG	AGTATGCTG	ATATATCTA
	TAACTGCAAT	TACCTGCTAA	CAAAACCGTG	GTTTTATGTT	CGCTGCTG	TTTATGCTG	CGCTGCTG	CGCTGCTG	AGTATGCTG	ATATATCTA
1101	TACGTTGGGA	GGTCTATATA	AGCAGAGCTC	GTTTATGCTG	CGCTGCTG	CGCTGCTG	CGCTGCTG	CGCTGCTG	AGTATGCTG	ATATATCTA
	ATCCACAGCT	CCAGATATAT	TGCTGCTGAG	CAATATCACT	CGCTGCTG	CGCTGCTG	CGCTGCTG	CGCTGCTG	AGTATGCTG	ATATATCTA
1201	CCCATCCAGC	CTCCGCGGCG	GGGATGCTG	CATTGCAAGT	CGGATTTCCG	GTGCTGCTG	GTGCTGCTG	GTGCTGCTG	AGGCTTTCTG	TGCTGCTG
	GGCTAGCTCG	GAGGCGCGCG	CCCTTGGCAC	GTAACTTTG	GGCTGCTG	CAGCTTTCTG	ACTCTAGAG	GTACCCAGCA	TCCCGAAGAC	AGCAGAGCTG
1301	TGCTGAGCTG	GACATGCTG	AGAAATCAG	GGTATGCTG	GGTATGCTG	GGTATGCTG	GGTATGCTG	GGTATGCTG	GGTATGCTG	GGTATGCTG
	ACCATCTGAC	CTGTTCAAGC	TCTTCTAGTC	CGCTGCTG	CGCTGCTG	CGCTGCTG	CGCTGCTG	CGCTGCTG	CGCTGCTG	CGCTGCTG
1401	TTTGTCTGTA	ACCTTGGCT	GGTGGAGAC	TCCTGAGGCT	TCCTGAGGCT	TCCTGAGGCT	TCCTGAGGCT	TCCTGAGGCT	TCCTGAGGCT	TCCTGAGGCT
	AAAGGACACT	TGGGACCGGA	CGACCTCTG	AGACTGCTG	AGACTGCTG	AGACTGCTG	AGACTGCTG	AGACTGCTG	AGACTGCTG	AGACTGCTG
1501	CCCTGTACAA	CACATGCTG	ACCTTGTACT	GGTGTGCTG	GGTGTGCTG	GGTGTGCTG	GGTGTGCTG	GGTGTGCTG	GGTGTGCTG	GGTGTGCTG
	GGGACATGTT	GTGTCACCGA	TGGGACATGA	CACATGCTG	CACATGCTG	CACATGCTG	CACATGCTG	CACATGCTG	CACATGCTG	CACATGCTG
1601	GTCCAAAGAG	AGGCGCGAGC	AGCTGCTG	TGGGAGGCT	TGGGAGGCT	TGGGAGGCT	TGGGAGGCT	TGGGAGGCT	TGGGAGGCT	TGGGAGGCT
	CAGGTTCTTC	TTCCGCGCTG	TCCGAGGAG	ACCGTGTGCTG	ACCGTGTGCTG	ACCGTGTGCTG	ACCGTGTGCTG	ACCGTGTGCTG	ACCGTGTGCTG	ACCGTGTGCTG

Figure 15A

pHRKad5-qag HEIG82

3301	TTGAGGACG CAGCTCCGC GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	Psil	TTGAGGACG CAGCTCCGC GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	TTGAGGACG CAGCTCCGC GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG
3401	AACCTCTGAC GTGCGAGCG GCGGCGAAGT GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	Psil	AACCTCTGAC GTGCGAGCG GCGGCGAAGT GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	AACCTCTGAC GTGCGAGCG GCGGCGAAGT GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG
3501	GAGGCGAAG TAGCGCGCG CTACTCTTCA ACTGCTGAG AAGCGCTGTT AACCTGAGG ACTGCGCTT AACCTGAGG ACTGCGCTT	Psil	GAGGCGAAG TAGCGCGCG CTACTCTTCA ACTGCTGAG AAGCGCTGTT AACCTGAGG ACTGCGCTT AACCTGAGG ACTGCGCTT	GAGGCGAAG TAGCGCGCG CTACTCTTCA ACTGCTGAG AAGCGCTGTT AACCTGAGG ACTGCGCTT AACCTGAGG ACTGCGCTT
3601	TCGCGCGAG CAGGCTTCTG CCGCTTCTG GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	TCGCGCGAG CAGGCTTCTG CCGCTTCTG GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	TCGCGCGAG CAGGCTTCTG CCGCTTCTG GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
3701	AGACGCGGTC GTCCAGAGC GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	Psil	AGACGCGGTC GTCCAGAGC GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	AGACGCGGTC GTCCAGAGC GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG
3801	GTGCTCTGCT GTCTTTATTT AGGCTTCTG GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	GTGCTCTGCT GTCTTTATTT AGGCTTCTG GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	GTGCTCTGCT GTCTTTATTT AGGCTTCTG GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
3901	CACAGACGA CAGAAATATA TCCCCAAAC GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	CACAGACGA CAGAAATATA TCCCCAAAC GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	CACAGACGA CAGAAATATA TCCCCAAAC GCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
4001	AAAGGTGACT CTGGAATGTC AGATACATG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	AAAGGTGACT CTGGAATGTC AGATACATG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	AAAGGTGACT CTGGAATGTC AGATACATG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
4101	TTTCCACTGA GACCTACAG TCTATGTAC CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	TTTCCACTGA GACCTACAG TCTATGTAC CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	TTTCCACTGA GACCTACAG TCTATGTAC CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
4201	GATCCAGTCG TAGCAGGAGC GCTGCTGAG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	GATCCAGTCG TAGCAGGAGC GCTGCTGAG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	GATCCAGTCG TAGCAGGAGC GCTGCTGAG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
4301	CTAGGTCAGC ATCGCTCTG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	Psil	CTAGGTCAGC ATCGCTCTG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	CTAGGTCAGC ATCGCTCTG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG
4401	CGGTTAAGCT GCGATGCGT CATAGCTG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	CGGTTAAGCT GCGATGCGT CATAGCTG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	CGGTTAAGCT GCGATGCGT CATAGCTG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
4501	GCCAAATCCA CCGTACCCAC GTATGCGCC CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	GCCAAATCCA CCGTACCCAC GTATGCGCC CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	GCCAAATCCA CCGTACCCAC GTATGCGCC CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
4601	TTGTTGTCAG AACCTGAGC ACATGTCAT CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	TTGTTGTCAG AACCTGAGC ACATGTCAT CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	TTGTTGTCAG AACCTGAGC ACATGTCAT CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
4701	ACCTCCAGCA TTGCTGCTG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	Psil	ACCTCCAGCA TTGCTGCTG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	ACCTCCAGCA TTGCTGCTG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG
4801	TTGAGGTTCT AAAGGTGAG ATAGGCTAT CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	TTGAGGTTCT AAAGGTGAG ATAGGCTAT CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	TTGAGGTTCT AAAGGTGAG ATAGGCTAT CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
4901	TTTCCAGGCA CAGCTTTGA CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	Psil	TTTCCAGGCA CAGCTTTGA CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG	TTTCCAGGCA CAGCTTTGA CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA AACACTGCG
5001	ACAGGTGCT ACTCTAGCAG TATGCTGTA CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	ACAGGTGCT ACTCTAGCAG TATGCTGTA CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	ACAGGTGCT ACTCTAGCAG TATGCTGTA CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
5101	CGAGTCTCTA AACGTAAAG GTGCGAAGT CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	CGAGTCTCTA AACGTAAAG GTGCGAAGT CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	CGAGTCTCTA AACGTAAAG GTGCGAAGT CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
5201	CTGCGAGGAA AGCAGTTTC TACAGAGTC CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	CTGCGAGGAA AGCAGTTTC TACAGAGTC CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	CTGCGAGGAA AGCAGTTTC TACAGAGTC CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
5301	GACCTCTCTT TCGTCCAGG ACTCTGCGAG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	GACCTCTCTT TCGTCCAGG ACTCTGCGAG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	GACCTCTCTT TCGTCCAGG ACTCTGCGAG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
5401	CAGCTGCGGT CATGCTGAG CAGGAGGTC ACTCTGCGAG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG	Psil	CAGCTGCGGT CATGCTGAG CAGGAGGTC ACTCTGCGAG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG	CAGCTGCGGT CATGCTGAG CAGGAGGTC ACTCTGCGAG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG
5501	GTGAGCGGCA GTAGGAGTC GTGCGCGCG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	Psil	GTGAGCGGCA GTAGGAGTC GTGCGCGCG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA	GTGAGCGGCA GTAGGAGTC GTGCGCGCG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG CCGCTTCCA
5601	GGGATAGCAG TTCTTCCAG GAAGCAAGT TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG	Psil	GGGATAGCAG TTCTTCCAG GAAGCAAGT TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG	GGGATAGCAG TTCTTCCAG GAAGCAAGT TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG
5701	CTCTATCTGC AAGACGCTTC CTTCGTTTCA AAAGTTTCC AAAGTTTCC AAAGTTTCC AAAGTTTCC AAAGTTTCC	Psil	CTCTATCTGC AAGACGCTTC CTTCGTTTCA AAAGTTTCC AAAGTTTCC AAAGTTTCC AAAGTTTCC AAAGTTTCC	CTCTATCTGC AAGACGCTTC CTTCGTTTCA AAAGTTTCC AAAGTTTCC AAAGTTTCC AAAGTTTCC AAAGTTTCC
5801	CCACAGCTCG GTACAGCTCT CTAGGCTAT TCGATCCATC ATATCTCTTC TTCTTCCAG TTCTTCCAG TTCTTCCAG	Psil	CCACAGCTCG GTACAGCTCT CTAGGCTAT TCGATCCATC ATATCTCTTC TTCTTCCAG TTCTTCCAG TTCTTCCAG	CCACAGCTCG GTACAGCTCT CTAGGCTAT TCGATCCATC ATATCTCTTC TTCTTCCAG TTCTTCCAG TTCTTCCAG
5901	GGTGTGAGC CAGTGTGAGG GATGCGGTAG AGCTAGCTCG TATAGGTTAG CCGCTCTTA GCTGCTGAG CATTCTGCT	Psil	GGTGTGAGC CAGTGTGAGG GATGCGGTAG AGCTAGCTCG TATAGGTTAG CCGCTCTTA GCTGCTGAG CATTCTGCT	GGTGTGAGC CAGTGTGAGG GATGCGGTAG AGCTAGCTCG TATAGGTTAG CCGCTCTTA GCTGCTGAG CATTCTGCT
6001	CCAGACGCGC CAGGCTCATG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG	Psil	CCAGACGCGC CAGGCTCATG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG	CCAGACGCGC CAGGCTCATG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG TTCTTCCAG
6101	GGTCTGCGCG GTCCCAATAC AGAAGGTCG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG	Psil	GGTCTGCGCG GTCCCAATAC AGAAGGTCG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG	GGTCTGCGCG GTCCCAATAC AGAAGGTCG CCGCTCTTA GCTGCTGAG CATTCTGCT GCTGCTGAG CTTCTCTGAG

Figure 15c

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4901	GTGCGCTTG AGGCTGTTC TCTGTGTCT GAAATGTCT CTAATGCTG CCG CTTCGC CTCTGCTGTC GCGGAGTATG CATTTCACCA TGGTGTCTATA GTCCAGTCTC
5001	CCACCGAAC TCCGACGAG AGTACGACGA CTTCGACAG GTCAGAGCG GTCAGAGCG CTCTGCTGTC GCGGAGTATG CATTTCACCA TGGTGTCTATA GTCCAGTCTC
5101	TCCGCGCTG GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
5201	TCCGCGCTG GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
5301	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
5401	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
5501	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
5601	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
5701	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
5801	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
5901	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
6001	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
6101	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
6201	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
6301	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT
6401	AGAGGCTCT GTCCGCTTC GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT GCGGACGCT

Figure 150

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6501 GCGTCACGCA CGAAGGAGGC GTAGAGATCG CGTAGCTTGT TACATAGATT GGTGTGATC TGCAGTCTA GGGGCGCTA GTCCAGGTTT TCTTTGATCA
 CCGAGTGGT GCTTCTCCGC CATCTCAGC GGTCTCAGC ACCTGTTGAG CTTCTACTG CCGGTGAT CCGGTGAT CCGGTGAT CCGGTGAT
 6601 TGTGATATCTT ATCTGTGCCC TTTTCTTCTC ACAGCTCTGAG GTTGTAGTAA AATCTTCTC GTTCTTCTC GTTCTTCTC GTTCTTCTC GTTCTTCTC
 ACAATATGAA TAGGACAGGG AAAAAAAGG TTTCTAGAGG CACTCTCTT TTTAGAGGG CCGAAGAGT CATGAGAAC TAGGCTTTGG GAGCTTCTC
 6701 CGAACGATTA GAGCTTAGCA TGTAGAGAG GTTACAGGTC TGTAGAGGT TTTTACGCTT TTTTACGCTT TTTTACGCTT TTTTACGCTT TTTTACGCTT
 CATTGCAATT CTGAGATCGT ACATCTTAGC CAACTGCGG ACCTATCTCT TCTATAGTAA AAGATGCTCA TCGGCGATAC GGAAGCGGCG GAGGCGCTT
 6801 GAGGTGTGGG TGAAGCGAAA GGTGTCTCTG ACCATGACTT TGAATTAATG GTATTGAGG TCGATCTGCT CCGATCTGCT CCGATCTGCT CCGATCTGCT
 CTCACACACC ACTGCTGTTT CCACAGGGAC TGTACTGAAA ACTTCATATC CATTAATCTT ACATACAGG GCGATAGG GCGATAGG GCGATAGG GCGATAGG
 6901 CCGTGTGCTT TTTGAGAGC GATTTGGA GGTGAGAGT GACATGTTT AAGAGTATCT TTTCTGCTG AGGATAGG AGGATAGG AGGATAGG AGGATAGG
 GGCACCGGAA AACCTTTGGC CTTAAAGCGT CCGCTTCTCA CTTTATGAC TTTCTATGAA AAGGCGGCG TTTCTATGAA TTTCTATGAA TTTCTATGAA
 7001 TCCGCGCACC TCGTACCGT TGTAAATAC GTGCGCGCGT ACATGATCTT TCTTAAAGC GTTGTAGTTC TGGGCGCACA TGTAAAGGTT TGTAAAGGTT
 AAGGCGGTTG AACCTTCCCA ACAATTAATG GTGCGCGCGT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 7101 GGGATGCGCT TGAATGAAG CAATTTTCTA AGTCTCTCTC TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 CCTTACCGGA ACTTACCTTCT CTTAAATAAT TCAAGGAGCA TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 7201 GGTGTGAGAG GAGGATAGAG CTCACAGGT CACTGAGCAT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 CCAACCTTGG CTGCTTACTC GAGGTGACCA GTGCGCGCGT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 7301 GGTGTGAGAG TGAAGGATTA GGTGTCTCTC TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 CCACTACGTC ATCTTCTCTT GGTGTGACCA GGTGTGACCA TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 7401 AACTTCAATG CCAAGATGAA GGTGTGACCA GGTGTGACCA TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 TTAAGTACT GTTCTTCTT PstI
 7501 CATGCGAGCC GATCGGAGG AACTGATCT CCGCGCACCA ATTGAGGAG TGTGATTTCA TGTGATTTCA GTTGTGATTT GTTGTGATTT GTTGTGATTT
 CTAGGCTCGG CTAGGCTCTC TTGACCTTGA GGTGCTGTTT TAACTCTCTC ACCGATTAAT ACACCACTTT CATCTTCTAG GACCTTCTCC GACCTTCTCC
 7601 GTGCTGCTT TTTTAAAGG GTGCGAGTA CTGCGAGTCT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 CACGACCGAA AACATTTTGG CACGCTCAT GACGCTGCC ACCTGCGGCA CATGTAGGAG GTGCTTCTCA TGGATCTCTG GCGCTTCTC CTTCTCTCTA
 7701 GGGAAATTTGA GCGCTTCTCC TGGCGGTTT GGTGTGTTT CTTTATCTT GGTGTGTTT GTTGTGTTT GTTGTGTTT GTTGTGTTT GTTGTGTTT
 CCTTTAACT CCGGAGCGG ACCGCGGAAA CCGACACCA GAGATGAGG CCGACGAACTA GAGATGAGG CCGACGAACTA GAGATGAGG CCGACGAACTA
 7801 GAGCACCGAC GCGCGGAG CCGAAGTCT AGATGCTGCG GGTGTGTTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT TCGATGATCTT
 CTTGTGTTG CCGCGGCTC GGTTTTCAAG TCTACAGGCG CTTCTCTCTA CTTCTCTCTA CTTCTCTCTA CTTCTCTCTA CTTCTCTCTA CTTCTCTCTA
 7901 CTGCGCGGCG GTACAGGTC GCGGAGTCT CTCACGTTT ACCTGCGATA GAGGAGTCT GAGGAGTCT GAGGAGTCT GAGGAGTCT GAGGAGTCT
 GAGGCGCGCG CAGTCTCAGT CCGCTTCTAG CCGCTTCTAG CCGCTTCTAG CCGCTTCTAG CCGCTTCTAG CCGCTTCTAG CCGCTTCTAG CCGCTTCTAG
 8001 TGTGTGTTG CCGCTGAT GGTGTGAG GGTGTGAG GGTGTGAG GGTGTGAG GGTGTGAG GGTGTGAG GGTGTGAG GGTGTGAG
 ACCAACCGCG CCGGAGCTA CCGAACGTT CCGAACGTT CCGAACGTT CCGAACGTT CCGAACGTT CCGAACGTT CCGAACGTT CCGAACGTT

Figure 15E

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9701	ACAAAGGCGT GGTATGCGCC CGTGTGATG GTGTAATTC AGTTGCTAT AACTGACGNG TTACGGTCT GGTACCGCG GGTACCGCG CACTGACGAG CACGCTCTCG AGCCATATG
9801	TCAGACGGGA GTAAAGCTTC GAGTCAAATA GTTACTGCTT GTAACTCTTC CAAAAATGTC GGGGCGGCT GGGGTAGAG ACTCTGCGCT CATTCGGAG CTCAGTTTAT GGTCTCACTA CCAATAGCTG GTTTTTCAG CCGCGCGGA CCGCATCTC
9901	GGGCCAGGCT AGGCTGCGCG GGGCTGCGAG GAGTCAATTA GGTAGATCT TCCATATTA TACCTGAGCA TCCAGTGAT GCGGCGGCG CCGGCTCGCA TCCGACCGGC CCGGAGCGCC CCGCTCTAGA AGTTGTATT CCGCTACTAT AGGATCTAC ATGGGACTTA AGGTCGCGC
10001	GTGGTGGAG GCGCGGAAA GTGCGGAGS GGTCTTCA TAATTGCGAG CCGCAAAAG TCGTCLATG TCGGAGGCT CTGGCGGCTC ATGGGAGCT AGCCCTGGA GACCGGCGG TCGGCGGCG
10101	AAATGTTGAC GTCTAGACG GTGCAAGG GTGCAAGG AGGCGTCT AGGCGTCT CTCTGCTGT CTGTGATA AATTCGAG GGTATCATG CGGACGAGCT CGGACGAGCT
10201	GGTTCGAGC CCGGTATCG CCGGTCTTC GTGATCCAG GTTATCCG CCGGTTCG CCGGTTCG AATTCAGT TCGGACGTA GACACCTAT TTAAAGCTT CCAATGACC GCGTCTCT
10301	TTTGGCTTC TTCAAGGCG AGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT
10401	AAACCGAAG AGGTCGCG CCGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT
10501	GTGCGGCTTC TCGGCGGCT CCGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT
10601	GGGCGGCTTC TCGGCGGCT CCGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT
10701	GGGCGGCTTC TCGGCGGCT CCGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT
10801	GGGCGGCTTC TCGGCGGCT CCGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT
10901	GGGCGGCTTC TCGGCGGCT CCGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT
11001	GGGCGGCTTC TCGGCGGCT CCGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT
11101	GGGCGGCTTC TCGGCGGCT CCGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT
11201	GGGCGGCTTC TCGGCGGCT CCGGCTGCT CCGGCTGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT GGTATGCT

Figure 15g

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11301	TCGATTTGAT	ANACATCTG	CAGAGATATG	TGATTCACGA	GTATATTTT	ATCTTCTG	ACATGCTT	CGCATCAAC	TATTCATGC	TTAGCTCTG
	AGCTAAACTA	TTTGTAGGAC	ACTCTTATC	AGATCTTCT	CTATTTTAC	TTTGTACG	TTTGTACG	CGGTATGTT	ATAAGTACG	ATCTGACT
11401	CAAGTTTAC	GGCCGACGA	TATATCTATC	CCCTTACTG	CTCATATACA	ACGATGTA	CACTGATG	TTCTATATC	GCATGCTCT	GAATTTCT
	GTCTAAATG	CGCGCTTCT	ATATCTATG	GGCAATGCA	GGTATCTT	TTTCTCAT	CTATCTCT	AGATGTACG	CGTACCCGA	CTTCCACG
11501	ACCTTGACG	AGCACTTGG	CTTTTATCT	ACGATGCA	TTCTATCT	CTATGCTG	ATCTGCTG	GGGACTCAG	CGACCCGAG	CTGATTCACA
	TGGAACTCG	TCTTGACCC	GCATATGCG	TTCTTCCGT	AGTGTCTCG	GCATCTGAC	TTCTGCTG	CGCTCGAGT	CGTGGGCTC	GACTACGTT
11601	GCCTGCNAG	GGCTCTGCT	GGCATGCA	GGCGATAG	ATGAGCTG	TCCTACTT	ACGCGGCT	TTACTTCTC	TGGGCTCCAA	GGCTACTGCT
	CGGACGTTT	CGGGACCGA	CGCTCTGCT	CGCTCTTATC	TTCTCGCTC	TCCTGCTG	TCGCGCTG	ACCCGCGTT	ACCCGCGTT	CGCTTGGC
11701	CTTGGAGGCA	GTCTGGGCG	GTCTGGGCG	GTCTGGGCG	GTCTGGGCG	GTCTGGGCG	GTCTGGGCG	GTCTGGGCG	GTCTGGGCG	GTCTGGGCG
	GGCTCTGCT	CGACCCGCG	CGACCCGCG	CGACCCGCG	CGACCCGCG	CGACCCGCG	CGACCCGCG	CGACCCGCG	CGACCCGCG	CGACCCGCG
11801	CGAGAGGAC	GGGAGTACT	AGCGGTATG	TTCTGATCA	GTATGATCA	GTATGATCA	GTATGATCA	GTATGATCA	GTATGATCA	GTATGATCA
	GGCTCTGCT	GGCTCTGCT	GGCTCTGCT	GGCTCTGCT	GGCTCTGCT	GGCTCTGCT	GGCTCTGCT	GGCTCTGCT	GGCTCTGCT	GGCTCTGCT
11901	CGTAACTCC	AGGAGGACT	GGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT
	GGATTTGAG	TGCTGCTGA	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT
12001	CTCTCTGCA	TTCTGAGC	GGTCTGCG	GGTCTGCG	GGTCTGCG	GGTCTGCG	GGTCTGCG	GGTCTGCG	GGTCTGCG	GGTCTGCG
	GAGAGGCTT	ANGCTTTG	CGACGAGCT	CGACGAGCT	CGACGAGCT	CGACGAGCT	CGACGAGCT	CGACGAGCT	CGACGAGCT	CGACGAGCT
12101	GGCCGACGA	GGCCGACCT	GGCTAGAG	GGCTAGAG	GGCTAGAG	GGCTAGAG	GGCTAGAG	GGCTAGAG	GGCTAGAG	GGCTAGAG
	CGCGCTGCT	CGCGCTGCT	CGCGCTGCT	CGCGCTGCT	CGCGCTGCT	CGCGCTGCT	CGCGCTGCT	CGCGCTGCT	CGCGCTGCT	CGCGCTGCT
12201	TCTGCGGAG	GGCTGCGCT	GGCTGCGCT	GGCTGCGCT	GGCTGCGCT	GGCTGCGCT	GGCTGCGCT	GGCTGCGCT	GGCTGCGCT	GGCTGCGCT
	ACACCGGCT	CGGACCGCT	CGGACCGCT	CGGACCGCT	CGGACCGCT	CGGACCGCT	CGGACCGCT	CGGACCGCT	CGGACCGCT	CGGACCGCT
12301	GTGCGCGCG	GTGCGCGCG	GTGCGCGCG	GTGCGCGCG	GTGCGCGCG	GTGCGCGCG	GTGCGCGCG	GTGCGCGCG	GTGCGCGCG	GTGCGCGCG
	CACCGCGCG	CTGCTCTCT	CTGCTCTCT	CTGCTCTCT	CTGCTCTCT	CTGCTCTCT	CTGCTCTCT	CTGCTCTCT	CTGCTCTCT	CTGCTCTCT
12401	ATTTTCTCA	GTCTGATCA	GTCTGATCA	GTCTGATCA	GTCTGATCA	GTCTGATCA	GTCTGATCA	GTCTGATCA	GTCTGATCA	GTCTGATCA
	TAAAGAGCT	CTGCTGATC	CTGCTGATC	CTGCTGATC	CTGCTGATC	CTGCTGATC	CTGCTGATC	CTGCTGATC	CTGCTGATC	CTGCTGATC
12501	CGCGCGGAC	GTGCTGATC	GTGCTGATC	GTGCTGATC	GTGCTGATC	GTGCTGATC	GTGCTGATC	GTGCTGATC	GTGCTGATC	GTGCTGATC
	GGCGCGGCT	CACGATGCA	AGGATGCT	GGTACGCT	GGTACGCT	GGTACGCT	GGTACGCT	GGTACGCT	GGTACGCT	GGTACGCT
12601	CTAGTCTCT	TCTGATCT	GTACGCTG	GTACGCTG	GTACGCTG	GTACGCTG	GTACGCTG	GTACGCTG	GTACGCTG	GTACGCTG
	GATCAGTGA	AGGATGCT	CATGCGCT	CATGCGCT	CATGCGCT	CATGCGCT	CATGCGCT	CATGCGCT	CATGCGCT	CATGCGCT
12701	AGGAGGAC	GGGAGGCT	GAGGAGGCT	TAAATCTCT	TAAATCTCT	TAAATCTCT	TAAATCTCT	TAAATCTCT	TAAATCTCT	TAAATCTCT
	TCTGCTGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT	CGCGGAGCT
12801	CAATTTGCG	TAGGAGGCT	AGGAGGCT	AGGAGGCT	AGGAGGCT	AGGAGGCT	AGGAGGCT	AGGAGGCT	AGGAGGCT	AGGAGGCT
	GTAAAGCG	ATGAGGCT	TCTGCTCT	TCTGCTCT	TCTGCTCT	TCTGCTCT	TCTGCTCT	TCTGCTCT	TCTGCTCT	TCTGCTCT

Figure 15H

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12901 GGCATGATATG CCTCAACAG GCGCTTTATC AACTGCTTAA TTATGACTT GATTCCTGTTT GTCGCTGTTA ACCCTGAGTA TTTCACCAAT GCTATCTTCA
CCGTATACAT GAGATTGCG CCGCAATATAG TTATGATAT ACCTGATA CTTATGCTATC GTCGCTGTTA ACCCTGAGTA TTTCACCAAT GCTATCTTCA
13001 ACCCGGCTG GCTACGCGC CCGCTTTTCT ACACGCTGTTT ATTCGATATG CTTATGCTATC GTCGCTGTTA ACCCTGAGTA TTTCACCAAT GCTATCTTCA
TGGCGCTGAC CGATGCGCG GACCAATAG TATGCGCGC TAATGCTGAC TATGCTGTTT GTCGCTGTTA ACCCTGAGTA TTTCACCAAT GCTATCTTCA
13101 TTCCCGCGAA CGCAGAGCC TGTAGATCT GTAAAGGCG GATTCGCTGTTT GTCGCTGTTA ACCCTGAGTA TTTCACCAAT GCTATCTTCA
AAGCGCGCTT GCGCTGCTGG ACATCTCAA CTTGCTGCG CTTGCTGCG TATGCTGTTT GTCGCTGTTA ACCCTGAGTA TTTCACCAAT GCTATCTTCA
13201 CTAGCGGCTG CCGCGCGCG GTCAGATCT AGTACGCTT TTCCAGTCTT GATTCGCTGTTT GTCGCTGTTA ACCCTGAGTA TTTCACCAAT GCTATCTTCA
GATCGCGGAC GCGCGCGCG CAGCTACGA TATGCTGCG TATGCTGCG TATGCTGCG TATGCTGCG TATGCTGCG TATGCTGCG TATGCTGCG
13301 AGGCGGCTA CTTAAACAC TCGCTGCTG ATCGCGCGC GGAAGGAGC CTTGCTGTTT GTCGCTGTTA ACCCTGAGTA TTTCACCAAT GCTATCTTCA
TCTGCTGCT CAGATGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG
13401 GATGATATG AGAGCTAGC CCGAGGCGA CAGGAGGCG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG
CTCATCTACC TTCTGCTGCG GCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG
13501 GAGGAGATG ACTGCGGAGA CGACAGGCG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG
CTCTGCTGAC TATGCGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG
13601 AAAAAAAG GATGATGCA AATTAAGAA CTTACCAAG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG
TTTTTTTTT CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG
13701 TATGAGAGGT CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG
ACTCTCTTCA GAGGAGGGA GATGCTGCT ACACCAAGC CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG
13801 GTGCTGCTG GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
CAGGAGGCG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG
13901 ACAGGCTGAC GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
TGTGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
14001 CACAGGAGC ATCAGCTG GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
GTGCTGCTG TATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
14101 AATAAGTTA AGGCGCGGT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
TTATTCATAT TCGCGCGCA CTTACGAGC GCGAGCGAT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
14201 ACTATGCTG GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
TATGAGGCT TATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
14301 GGTAAAGTTT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
CGATTTTCAA CTTGCGCGGT TATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
14401 ATTTGCTG CNGATGCGT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT
TAAAGGAGC GTCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG CCGCTGCTG

Figure 15I

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14501 CCTACGATGA TCTGGAGGCT GATACATTC CGCAGCTTT GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 GATATCTACT AGACCTGCA CCAATGTAA GCGCTTAA GCTACACTG CCAATGTAA GCTACCTTGA GCGTATGCTG CCGTATGCTG
 14601 AGGAGGAGC AACAGAGTG GCAAGGCGC GATACCTTGA GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 TCGCGCTGCG TTGCTGTCAC CGTACCTTGA GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG CCGTATGCTG
 14701 GCGGACACCT TTGCGACAGG GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG CCGTATGCTG
 CCGCTGTGGA AACGCTGTC CCGACTGCT GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 14801 AGAAGAAACC GGTGATCMAA CCGCTGACAG AGTACGCA GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG CCGTATGCTG
 TCTTCTTTGG CCACTAGTTT GCGGACTGTC TCGTCTGCT CCGTATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 14901 CCGTGTATAC AACTAGGCG ACCCTGACAG CCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 GGAAGCTATG TTGATGCGC TGGAGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 15001 TTGCGAGACA TGATGCAAGA CCGCTGAC CCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 AACGCTCTGT ACTACCTTCT GCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 15101 GCTTCTTACA GAGCAGGCG GTCTACTGCC AACTATGCG TTGATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 CGAAGATGTT GCTGCTGCG CAGTGTAGCG TTGATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 15201 CCGCGACCC CCGACATCA CCGCTGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG CCGTATGCTG
 GCGCGCTGCG GCGTGTAGT GCGTGTAGT GCGTGTAGT GCGTGTAGT GCGTGTAGT GCGTGTAGT GCGTGTAGT GCGTGTAGT
 15301 GTGACCATTA CTGACGCGAG ACCTGCGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG CCGTATGCTG
 CACTGCTTAT GACTGCTGTC GCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 15401 GATGCTCAT CTTTATATCG CCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 CTTACAGGTA GGAATATAGC GCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 15501 AGTGGCGTG CCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG CCGTATGCTG
 TCACGCGAC GCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG CCGTATGCTG
 15601 GAGGCGGCA ACTACAGCG CCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 CTGCGCGCT TTGATGCTG GCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 15701 GACGCGGAG GCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG CCGTATGCTG
 CTGCGCGCT SRI
 15801 ACAGGCGCC ATGCGGCGC CCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 TCGCGCGCG TACGCGCGC GCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 15901 AGTGTATGA CTCAGGCTG CAGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 TCAGGCTAT GAGTCCGAG GCGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 16001 TTGCAAGAA AACTACTTA GACTGCTG GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG
 AACGCTCTTT TTGATGAT CAGGCTGTC GCGTATGAC GATATGAC GATACCTTGA AGATGACAC GAAAGAGCG GCGTATGCTG

Figure 15J

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16101	CCAGGTGATC GCGCGGAGA TGTATGTC CCGGAGAGAG GAGAGACAGG ATTATAGCTA GCGGAGTCA AAGAGAAAA GNAAGATCAT GGTCCAGTAG CCGCGCTCT AGATACCGG GGGCTCTTC CTATATCTTC TAATATCTTC GACTTTGAT TTGCGCACT TTTTCTTTT CTTTCTACT
16201	GATGATGAG TTGAGGACGA GGTGAAATG GTTACACCTA GTTATCTCAG GTGAGCTTTA CATTGGAAG GTGAGGCTT AATAGCTTT TTGCGACCC CTACTACTTG AACTGCTGCT CCACCTTGAC GACTGTGAT GTGCTGGTC CCGTCCAT GTGACCTTC CAGCTGCGCA TTTTGCACAA AACCTGCTT
16301	GCACCACTGT AGTCTTTAG CCGCTTAGG GCTCCACCG CACTACAG GCGCTTTATG ATGAGGTATTA GAGCGAGCTG GACTGCTTG AGCAGGTCAA GCTGCTGCA TCAGAAATGC GTGCTACTTG GTAGGTGAG GTGAGATGTC TACTGCACAT GCGCTGCTC CTGAGGAACT TGTGCGGTT
16401	CGAGGCGTC GAGGAGTTTG CTTACCGAAA GCGGATAG GACATCTTGG GTTGTCTGCT GTACAGGTTC ACCCGAAC CTAGGCTAAA GCGCGTAACT GCTGCGGAG CCGCTCAAC GATGCGCTTT GCGGTATTC CTGTACGACC GCAATGCTA CCGTCTCCG TTGGGTTG GATCGGATTT CCGGCTTTGT
16501	TTGCTGCGGC GCTTGTACCG TCGGAGAAA AGCGGCTCT AAGATGAG TTGCTGACT TGGGACGAC CCGTGTACT ATGCTTACCA GACGTGCTCC AGAGCGGCT CCGAGGTGCG AGGCTCTTT TCGCGCGTAA TTTGTGCTC ACACCACTGA ACCGTGGTG GCACGTGCT TACCATGCT
16601	AGCGCCAGCG ACTGGAAGT GTCTTGAAA AATGACGCT GGAACCTAG GTGCAACCCG GACTCGGC CACAGAGGCT GCGCGCTGA TCCGCTGCG TCACTTCTA CAGAACCTTT TTTACTGCA CTTTGACTC GTTGTGCTC TCCNCGGCA CCGCGGTTAG TTGCTGCACC GCGCGCTGA
16701	GCGGCTGACG ACGGTGACG TTTGAGTACC CACTACAGT AGCAACCTA TTGCAACCG CACAGAGGCT CACAGAGGCT GGTTCGCTCA CCTGCACGTC TGGCACTGC AAGTCTATG GTGATGTCTA TCGTGTGCT ACGGTGGCG GTGCTGCTG GTGCTGCTG TTTGAGGCG CCAACGAGT
16801	GCGGTGCGCG ATGCGCGCT CCGCGGCTC GCTGCGGCG CCGTCAATAC CTTTACGAG GTGCAACCG GTGCTGCTG TACCGGCTC TCAGCGCTC CCTGCACGCG TACGCGGCA CCGTGGCG CCGTGGCG CCGTGGCG GCTACTGCT GAGATGCTC CAGCTTTGCG TGGGACCTA CAAAGCGCA AGTGGGCG
16901	GCGGTGCGCG CCGTTGAGG AAGTACGCG AAGTACGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCTGCACGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG
17001	CACCTACGCG CCGAGAGAC GAGCACTAC CCGAGCGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG GTGATGCGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG
17101	GTGCGCAGCG TGGCTGCGCA AAGAGCGAG ACCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CAGCGCTGCG ACCGAGCGCT TCGTCCGTC TCGGACCAAG ACGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG
17201	ATATGCGCT CAGCTGCGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG TATACCGCGA GTGAGCGCG GAGCGAAG GCGAGCGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG
17301	GCGTGGCG CAGCAGCGCG GCGCGCGCG GTGAGCGCT GTTACCGCT CTAATGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CAGCGCGCG GTGAGCGCG CCGCGCGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG CCGTGGCG
17401	GTGCGCGGAA TTGATGCGCT GCGCTTTCAG GCGCAGAC ACTGATTA ACGAGTTTC ATGTGAAAA ATCAAAATTA AAGTCTGGA CTTCTACGCT CAGCGCGCTT ACGTAGGCA CCGGAGCGT CCGTGGCG TCGATTAAT TTTCTCAAC TACACCTTT TAGTTTTAT TTTGAGACT GAGAGTGGCA
17501	GCGTGGCG GTTACGATTT TTGTAGATG GAGCATCA ACTTGGTC TCTGCGCG CCGACGCT CCGCGCGCT CATGCGGCTT CATGCGGCTT TGGAGATTA GCGACCGAG ACATTGATA ACATCTTAC CTTCTGTAT TGTAAAGCAG AGACCTGAC GCTGTGCGA GCGCGCGAA GTACCGCTTTG ACCGTTCTAT

Figure 15K

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19301	AGACCTAATG	GGCCACAAAT	CTATGCTAA	CAGGCTAAT	TACATGCTT	TTATGATTA	TTATATGAT	CTATGATAT	ACACAGCAC	GOSTAATAT
19401	TCTTGATTA	CCGTTGTTA	GATACGGTT	GTCCTGTTA	ATGTAACGA	AACTCTCTT	AAATATCTA	GATATACAT	TGTTGTCGT	CCCATTTAT
19501	GGTGTCTGG	CGGCGCAAC	ATCGTACTG	ATGCTGTTG	TAGATTGCA	AGACAGAAC	ACAGAGCTT	CATACCACT	TTCTGCTAT	AGSTAACTG
19601	CCACAGACC	GGCGGTCTG	TAGGCTCAAC	TTAGAGCAAC	ATTTAAATCT	TCTGCTCTT	TGCTCTGAA	TATGCTGCA	AACTAACTG	AGSTAACTG
19701	ATAGAACCA	GTACTTTCT	ATGCTGTTG	ATGCTGTTG	CAGTATAT	CGCATCTTA	CGATATAT	AAATATCTA	ACTGACATG	AACTTCCAA
19801	TATCTGCTG	CATGAAAGA	TACACTTTG	TCGCAACT	GTGATATTA	ATTTGAT	TTATATCTA	TTATATCTA	TGACTTCTG	TTGAAATTT
19901	TTACTGCTT	CGACTGAG	GTGCTGTTA	TACAGACT	CTTACAGG	TAAACCTTA	AAATATCTA	AAATATCTA	GGGAAAGA	TGCTACAGAA
20001	AAATGCTAT	TTTACTTTA	TTCTCACT	CACACTAAT	ATGCTCTTA	AAATATCTA	AAATATCTA	AAATATCTA	CCCTTTCT	ACCATGCTT
20101	TTTCTGATA	AAATGAAAT	AGAGTTTGA	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT
20201	AAATGCTAT	TTTACTTTA	TTCTCACT	CACACTAAT	ATGCTCTTA	AAATATCTA	AAATATCTA	AAATATCTA	CCCTTTCT	ACCATGCTT
20301	TGTAATGCT	CGACAGCTA	AGTACAGTC	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT
20401	ACATAAAGG	GCTGTTGAT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT
20501	GGTATGAGC	TGCTACATTA	ACCTTGAGC	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT
20601	CGATCACCT	ACCATGTAAT	TGCACTCTG	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT	TTCTCACT
20701	CGCTCAATG	TGCTGAGCA	TGCTGAGCA	TGCTGAGCA	TGCTGAGCA	TGCTGAGCA	TGCTGAGCA	TGCTGAGCA	TGCTGAGCA	TGCTGAGCA
20801	CGGAGTTACA	ACGACCTCT	ACGACCTCT	ACGACCTCT	ACGACCTCT	ACGACCTCT	ACGACCTCT	ACGACCTCT	ACGACCTCT	ACGACCTCT
20901	ACGCTTACG	GTGAACTG	GTGAACTG	GTGAACTG	GTGAACTG	GTGAACTG	GTGAACTG	GTGAACTG	GTGAACTG	GTGAACTG

Figure 1SM

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[illegible]

Figure 15N

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22601 ATCTTGCCCT TACTAGACTG CTCTTTTACG GCGCTCTACG CTTCTTTGCT GTCTACATCC ATTCAATCA CGTCTCTCTT ATTATTCATA ATGCTTTCCCT
 TAGAACCGGA ACCATCTGAC GAGTAAATCG CCGCGAGTGG TCCNAAGCTA GCGCTCTACG TAAATGTTAGT GCACGAGGA TAAATAGTAT TACGAGCTCA
 22701 GTAGACACTT AAGCTCCCT TCGNTTYAG TCGAGCTGTS CACTACAC GCGGACCTGS TCGGCTCTCG ATGCTTTCTAG GTACCTCTCG CNAATGATG
 CATCTGTCAA TTGAGCGGA AGCTAGACTC GCTCTGCCAC CTATATTTTG CTTCTCTTTC ACCGCTCTAC TACGACATC CAGTGGACAG GTTTTCTCAN
 22801 CAGCTACGCC TCGAGGATC GCGCTCATAT GCGCTCATAT GCTCTTTTTC TGTCTGAGCT CAGCTCTAAC CCGGCTCTCT CCTGCTTTCT CCAAGCTCTT
 GTCCATGCGG ACCTCTCTAG CCGCTGATGA GCGCTGTTTC CAGACACAGT ACCACTTTCA GCGGCTCTCG GCGGCTCTCT GCGGCTCTCT GCGGCTCTCT
 22901 CATACGCGCG CCGAGCTTC CACTCTCTCA GCGCTGATGT TTAAATTTTC GTTATCTAGT TTATCTACCT GGTACTCTCT CATCAGCGCG CCGGCTCTCT
 GTATGCGCGG GGTCTCGAAG GTGACCACT CCGCTCATCA ACTTCAAGCG GAATCTTAC ATATGCTGCA CCGTCTCTCT GTAGTCTGCG GCGGCTCTCT
 23001 CCGTCCCTCT CTCTACCGA GACACGATCG GCGCTCTCT GCGCTCTCT ACCTTAAATT CACTTTCTCG TTCTCTCTCT TCTCTCTCT CCGGCTCTCT
 GGTACCGGAA GAGGCTCTCT CTCTCTCTCT GCGCTCTCT GCGCTCTCT TCGCTATTAA TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT
 23101 CCGCTATCCA CCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 GCGCTATGCT GCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 23201 ACCATTCTGA GCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 TCGTAAACAT CCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 23301 TCTTGGGCGG ATGCGCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 AGAGCTCTCT TCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 23401 CTGCTATGCG GCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 GAGCTATGCG GCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 23501 GCGGCTCTCT GCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 GCGGCTCTCT GCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 23601 AGAGGAGCAG CCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 TCTTCTCTCT GCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 23701 GCGGAGGAGGA GTGATTTATCG AGGAGGAGG CCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 CCGGCTCTCT CACTATATAG TCGGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT GCGCTCTCT
 23801 GCGAGGCGAA AGGAGGAGG AGGAGGAGG AGGAGGAGG AGGAGGAGG AGGAGGAGG AGGAGGAGG AGGAGGAGG AGGAGGAGG AGGAGGAGG
 CCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT
 23901 GCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT
 CCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT
 24001 ACCGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT
 TCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT CCGGCTCTCT
 24101 TTTTCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT
 AAGAGGCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT TCGGCTCTCT

Figure 15D

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24201	CGTGGCTCAA CGAGGTGCA AAGATCTTTG AGGTTTCTTG AGT GAGGAG AATGAGGATG CAAAGCTATCT GAGCAGGAGAA AACAGCGAATA ATGAAAGTTCA GGAGCGAGTT GTTTCACGGT TTATTAGAAC TCCAGAGAC TGGAACTGTC TTGAGAGGCG GTTTCAGAGA GTTGTGCTTT TGTGCTGCTT TACTTTTCAGT
24301	CTCTGGAGTG TTGTGGAGAC TGAGAGGTGA CAGCGGCT CTAGCTCTAC TAAATCTAG CATGTAGTTC ACCACTTTTG ACCAGCCGCG ACTTAAAGCTTA GAGACTCTAC AACCACTTTG AGCTCCCACT GTTTCAGGCG GATGTAGATG AATTTCCTGC GTAGCTCCAG TGGGTGAAAC GGTATGGGCG TGAATTTGGAT
24401	CCCCCAAGG TGTATGAGAC AGTCAATAGT GAGTGTATG TGTGTCTGTC GAGTCTCTGC GAGAGGATG CAATTTTGA AGAACAAACA GAGGAGGCTT GGGGGCTTCC AGTACTCTTG TCACTACTCA CTGCACTAGC ACATGTGACG GTCTGCTTAC CTCTGCTTAC GTTAAACGT TCTTGTTTGT CTCTCTCCCTA
24501	TACCCCAAT TGGCAGCAG CAGCTAGGCG GCTGCTTCA AAGTGTGAG GTGAGTGAAG AGCGAACTA ATGATGAGCG CAGTCTCTGT ATGGCGTCA ACCGCTCTC GTGATCTCG CGACCGAGT TTGTGCGCTC GGAGCGCTGA ACCTGCTGCG TGGTTTGTAT TACTTACCGCG GTACAGGAGCA
24601	TACCGTGGAG CTGTAGTGA TGACGGGTT CTTTGCTGAC CCGGATGTC AGCGTAGCT AGAGTAAACA TTGCACCTACA CTTTTCGACA GGGCTACGTA ATGGCACTC GAACTCACT AGTCCGCA GAAACGACTG GGGCTCTAG TCGGTTTGA TCTCTTTTGT AAGGTGATGT GGAAGCTGT CCGGATGCT
24701	CGCCAGGCTT GCAAGATCTC CAACGTGGAG CTCTGCAACC TGCTCTCTTA CTTTGTGAAT TTGCAGGA ACCGCTTGG GCMAAGCTG CTTCATTTCA GGGTCCGGA CTTTCTAGAG GTTGCACCTC GAGAGCTTGG ACCATAGCAT GAAACCTTAA TACGTCTTTT TGGCGAACC CGTTTTCGAC GAATTAAGT
24801	CGCTCAAGGG CGAGCGGCG CGCGACTAG TCGCGACTG CGGCTGATC AGCGCTGAC GCMAATCAAT AAGATAGCA TGTGTAGCGT CTGCGCTTAC CCGCAACCG TGGTCACGAA CGAGTTCCC GCTCCGCGG GCGCTGATC AGCGCTGAC GCMAATCAAT AAGATAGCA TGTGTAGCGT CTGCGCTTAC CCGCAACCG TGGTCACGAA
24901	GGAGAGTGC AACCTCAAGG AGCTGACGAA ACTGCTAAG GNAACTTGA AGTACCTATG GACGCTTTC AACGAGCTT CCGTGGGCG GCACTGTGT CTCTCTCAG TTGGAGTTCC TGACGCTTT TGACGATTTT CATTGAACT TCGTGTATAC CTGCGGAG TGGCTGCGA GGCACCGCG CGTGGAGCG
25001	GACATCAAT TCCCGGAGG CCGTCTTAA ACCCTGCAAC AGGCTCTGCC ATGCTCAAGCA AGTTCAAGCA TTGTGAGAA CTTTAGGAACT TTATCTCTA CTGTAGTAA AGGGGCTTGC GGAATTAAT TTGAGAGTTG TCCAGAGCG TCTCAAGTGG TCACTTTCTT ACNACGCTT GAAATCTTTG GAATAGGAT
25101	AGCGCTAGG AATCTTCCC GCGCTCTCT GTGCACTTCC TACCGACTTT GTGCCAATTA AGTACCGCA ATGCCCTTGG CCGCTTTTGG GCGACTGTCTA TGGGAGTCC TTAGAACCG CGGTGAGCA CACGTGAAG ATCCCTGAAA CACGGTAAAT TCATGGCGCT TACGGGAGCG GCGGAAACCC CGTTACCGAT
25201	CTTCTGCGAG CTAGCCAACT ACCTTGCCA CCACTCTGAC ATATGAGAG AGGTAGCGG TGACGTCTTA CTGGAGTGT ACTGTGCGTG CAACTATTC GGAGAGGTC GATTCGTTCA TGGAACGAT GTTCAGACTG TATTACCTTC TGCACTCTCC ACTGCCAGAT GACTCTCAG TACACAGCGAC GTTGTATAT
25301	ACCGCGGACC GCTGCTCTGT TTGCAATTCG CAGCTGCTTA AGCAAGTCA AATTATCTT ACCTTGAGC TGCAGGGTCC CTGCGCTGAC GAAATGTCCT TGGCGCTCG CGAGGAGCA AACGTTAAGC GTTCAGCAAT TGCTTTTCAGT TTAAATAGCCA TGGAAACTCG AGCTCCAGG GAGCGGACTG CTTTTATGG
25401	CGCTCCCGG GTTCAAACTC ACTCCGAGG TGTGAGCTC GCTTTACTT GCAAAATTTG TACTTAGGA CTACAGCTC CACGAGATTA GGTTCCTAGA GGCAGGCCC CAATTTTATG TGGGCGCG ACACCTGAG CCGAATGGAA GGGTTTAAAC ATGCACTCTT GATGTGCGG GTGCTCTAAT CCAAGATCTT
25501	AGACCAATCC GCGCCGCTA ATCGGAGCT TACCGCTGC GTTATTAGC AGGCTACAT TCTTGTGCAA TTGCAGGCA TCAACAAAGC CCGCCAGAG TCTGTATAG GCGGCGGAT TACGCTTGA ATGCGGAGT CAGTAATAG TGGCGTTTA ACAAACGGTT ACGTTTGGT ACGTGTTCG GCGCTTCT
25601	TTTCTCTAC GAAAGTACG GGGGTTTAC TTGACGCCCC AGTCCGCTGA CAGCTCTAAC CCAATCCCC CGCCCGCGA GCGCTATACG CAGCAAGCT AAGACGATG CTTTCTCTG CCGCCCAATG AACCTGGGG TACGCGCGCT CCTCGATTTG GCGGTAGTC CCGGATAGTC GTGCTGCGG

Figure 15P

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27301 CCTCCGCGCC ACTATCCGGA TCATTTTAT CTTCACCTTTG ATG GTAAA GCACTGCGCG GACGCTACG ACTGAATGTT AAGTGGAGAG GCAGAGCAAC
 GAGGCGCGG TGATAGCGCT AGTTAATATA GGATTGGAAC TGG TATTTT CCACTGAGTTC CTATCTATTC TTACTTACAA TTCACTCTC GGTCTGCTT
 27401 TCCCTCTGAA ACACCTGCTC CACTGTGCGC GGCACAAATG CTATTCCTCT GACTTCGCTG ATTTTCTGT CTTCACCTAC TTTCTTAACT
 ACCTGACTT TGTGACCCAG GTGACACGCG CGGTGTTCAC GAAATCTGCG CTGACGCCAC TCTTAACGTA GAACTTAACT GGGCTCCCTAG TATAGCTCTT
 27501 CCGCGCGCAC GCGTTCGCGC TTACCGCTCA GCGAGACTTT GCGCTATGTC TGAATCGGGA GTTTACCCGAG CCGCCCTCTG TAGTTGACCG GCACAGCGTA
 GCGCGCGCTG CCGCAGCGCG AATGCGCGGT CCGCTCTGAA CCGCATCGG ACTAAACCTT CAATGGGTG GCGGGGAGCG ATCACTCTGC CCGTCTCCG
 27601 CCGTGTGCTC TCACCTGTGAT TTGCACTGT TTGCACTGT CTTAACCTGT CTTAACCTGT GATTACATCA AGATCTTCTT TCGCATCTCT TATATAATAC AGNAATTA
 GGBACAGAG AGTCACACTA ACGTTTCA CAATCTGAC GATTGCGAC CTAAATCTAGT TCTAGAAACA ACGGTAGAGA CACGACTCAT ATTATTATG TCTTTAAT
 27701 ATTAATCTGG GCTCTATGCG CCATCTCTGA ACGCTCACCG TCTTCACCGG CCGTAAGCAA CCGTAAGTAA CCGTCTCTG TACTTTTAACT ATCTCTCG
 TATATGACCC CGAGATAGCG GGTAGGACAT TTGCGGTGCG AGATGCGGC GGTTCGCTT GGTTCGCTT GGAATGAGC ATGAATAATG TAGAGAGGTA
 27801 CTGTGATTTA CAACGATTTT ACCCAGACG GATGAGTCT ACATGAGAC CTCTCCGCGC CTCTGACTC CATCAAGAAA AACCCACCC TCTTTACCT
 GACACTAAT GTTGTCAAG TTGCTCTGCG CTCACCTAGA TCGTCTCTTG GAGAGGCTCG AGTGGATGAG GTAGCTTTT TTGTGCTGAG AGAATGAGC
 27901 CCGGACCTT ACATGCTGCT CACCGCGCGC TTACACCAAC CTACCGCTGT ACCCTTAACC AGCTTTTTC CCGACAGACC TCANTAACTC TGTTTACCA
 GCGCTTCCA TCTTCACCGA GTGCGCGCG GTGCGCGCG GATGCGGAC TCGCATTTG TCTGAAAAAG GCGTCTCTG AGTTATTGAG ACNAATGCTC
 28001 AACAGAGGT GAGCTTACGA ACCCTTAGG GTATTAGCG AAATGCGCAG CTACTGTGCG GTTTATGAG AATTCAGCA ACTTACGCG CTATCTTAAT
 TTGCTCTCCA CTGGAATCTT TTGGAAATCC CTTAATCTCG TTTCGCGCTC GATGACACCC CAATACTTG TTAAGTTCTT TGAATGCGC GATATGAT
 28101 TCAGCTTCTT CTAGAACTCG GGTGCGGT ATTCTCTG TCATGATCTT ATACTAACCC TTCTCTGCTT AAGGCTGCGC GCTCTCTT
 AGTCCAAAGA GATCTTAGCC CCAACCCGAA TAAGAGACAG AACACTAGA GAATTAAGAA TATGATGCG TAGAGAGCGA TTCCGAGCGG CCGACGAC
 28201 TCGACATTTG CATTTATGCT CAGCTTTTAA AACCTGCGG TCGCCACCCA AGATGATAG GTACATAATC CTAGGTTTAC TCAGCTCTGC GTACGCTCAC
 ACGTGTAAAC GTAAATACGA GTCGAAAT TTGCGACCC TTGCGACCC AGCGTGGGT TCTACTAATC CATGTATTAG GATCCAAATG AGTGGAGCG CAGTGGGT
 28301 GGTACCAACC AAAGGTGGA TTTTAAGGAG CCAAGCTGTA ATGTTACAT CTCACTGTA CCGACTGCT GTTAATGCT GCACCACTCT TATAAATGC ACCACAGN
 CATGCTGCGG TTTTCACTT AAATCTCT GGTGCGCAT TACAATGTA CCGTGGACTT CGATTACTCA CCGGTGAGGA ATATTTTACG ATATTTTACG TGGTCTCTT
 28401 ATGAAGCT GTTATTCG CACAAACGA AAATGCGAA GTATCTGCT TATGCTATTT GACAGCGAG TCACACTACA GATATATAG TTACAGTTT
 TACTTTTGA CCAATAAGCG GTGTTTTGT TTTAACCTT CATACGCAA ATACGATAAA CCGTGGTCC ACTGTGATGT CTCATATTAC AATGTCAAAA
 28501 CCAAGGTAAA AGTCATAAA CTTTATGTA TACTTTTCCA TTTATGAAA TGTGCACT TACCAGTAC ATAGCAAAC AGTATAGTT GTGCGCGCA
 GGTCCCATTT TCAGTATTTT GAAATACAT ATGAAAGGT AATATCTTT ACAGCTGTA ATGCTACAT TACTGTTTG TCATATTCAA CACCGTGGGT
 28601 CAAATTTGT TGGAAACAC TGCTCTTTC TGCTGACTG CTATCTAAT TACAGTCTC GCTTGTGCT GTAGCGTACT CTATATTAAA TACNAAGCA
 GTTTTAACAC ACCTTTGTG ACGGTGAG AGCAGCTGAC GATACATTA ATGTCACGAG CCAACCGAGA CATGGATGA GATATATTT ATGTTTCTC
 28701 GACGAGCTT TATTGAGGA AAGAAATGC CTTAATTATC TAGTTACAA AGCTAATTC ACCACTAAT GCTTTACTCG CCGTCTGCAA AACNAATTA
 CTGCTGCAA ATAACTCTT TTCTTTTACG GAATTAAATG ATTCATCTT TCGATTACAG TGGTATTA CCAATGAGC GAAATGAGC GACCAACTGT TTGTTTAA
 28801 AAAGTTAGC ATTAATTA GAATAGATT TAAACCCCG GCTCATTTTC TCTCTAATAC CATTCCTG ACANITGAC AATATGAG TCTATGCGG ATATCTCTA
 TTTTCAATCG TAATATTAAT CTTATCTTAA ATTTGCGGG CCACTAAGG AGGAGTTATG GTTAGGGAC GTATTACTG AGATACACCC TATPACCGGT

Figure 15R

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28901 GCGCTACAC CTTGAAGTCA GCGTTCCTAG AGGTAGAGAT CTGACTTTGG CCAAGACCTG TCCCGCGAT TTGTTCCAGT CCACATACAG CCACCCACCTC
 29001 CCGGATGTTG GAACCTCAGT CCGAGAGATC TACAGTCTGA GACTGAGACC GGTGGTGTAC AGGCGGCTA AACAGGCTCA GGTTCATGTC GCTTAGGTAT
 29101 TAAACAGAT GACACACACA ACCACAGCG CCGCGGTAC CCGGCTTACA CCGGCTTACA TATACACCAA AGTTCTGCC ATTTCTGACC TTATCAATTA TCACCATTA
 29201 ATTTCTCTA CTGTTGTTGT TGTTCGCTCC TGTTCGCTCC GGTGGGATG GTGCTGCTCC TATGTCGCTT CATTCTGCTT CATTCTGCTT CATTCTGCTT
 29301 GAAACCGTAC ACCACCAAGA GGTATCGGCA ATACACCAAT AGCAATAT TGTATAGAT GTACGAGATG AACACATGT TCTTTCTCT TACAGTATCA TTAATATGAA
 29401 TATAGTCCA TCAATGTGCT ACACCCAAAC AATGATAT TGTATAGAT TGTATAGAT TGTATAGAT TGTATAGAT TGTATAGAT TGTATAGAT
 29501 ATATCAGGCT AGTACACCA TGTGCTTTTG TTACTACTCT AGGTATCTTA CCGCTGCTAC TTTCTGTACA AGAAAGAGA ATGTCATCT AATTACTCT
 29601 CAGCATTCCT CAGTTTCTTA TATTACTGAC CCGTCTGCG CTTTCTGCG CTTTCTGCG CTTTCTGCG CTTTCTGCG CTTTCTGCG CTTTCTGCG
 29701 GTACTAAGA GTCATAAAT ATATGACTG GAAACACAC GAAACACAC GAAACACAC GAAACACAC GAAACACAC GAAACACAC GAAACACAC
 29801 GCGTTACAG TCTATTGCT TTACGATTT GTACCCCTCA CCGTCTGCG CCGTCTGCG CCGTCTGCG CCGTCTGCG CCGTCTGCG CCGTCTGCG
 29901 CCGAATGTC AGATAACGA AATGCTTAA CAGTGGAT GCGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG
 30001 GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG
 30101 GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG
 30201 GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG
 30301 GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG GTGATGACG

Figure 155

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32101	TAACATGTC AGTCAGTTT ACTTAACCG AGCAAAACT AAACCTTAA CACTAACAT TACACTAAAC GGTACACAGG AMACAGAGA CACAACCA
32201	ATTGTAACAG TCGTTCAAA TGAATTTCC TCGCTTTTGA TTTHAGNTT GTCATTTGTA ATGTATTTTG CCATGTGTCC TTGTCTCTCT GTGTTGAGT
32301	AGTGTACT CTATGTGAT TTCAATGAG TTCTGTGCTT ACATTAACAT TTTCACAT TTTCACAT TTTCACAT ATTGCECAV
32401	TCACGTATGA GATACAGTAA AAGTACCTG AGCAGACCG TGTGTATTA ATACTTTAT AAACCTTGA GAGAAATGTA TAACCTTTT
32501	AAATAAGAA CTGTTGTGTT AGCTTCAAC GTCATTAAT TTCAATTTTA GAAATTTTA CAAATTTTA CTAATGCTAT ATATCGGCTT GGTGTTGTA
32601	CTTATACAG ATCAGGTAC CTTAATCANA CTCACAGAC CTTAGTATTC AAATTTTCA CTTTAACT TCAATTAATA TCAATGCTAT ATATCGGCTT
32701	CGATATGTC TAGTGTGAT GAAATTAATTT GAGTGTCTTG GGAATCAATG TTGAGCTGTT GAGGAGGCTT TGTGTCTCTC ATGTGTCTAG AATGAGGCT
32801	GTGTGCTTTA AAAGCATCA TATCATGGT AACAGACATA TTCTTATGTT TTAATTTCA CAGCTTTTTC TGTGTGAGGA AACGCTCATC AGTGTATTT
32901	CGACCGAAT TTTCGTAGT ATAGTACCA TTCTGTCTAT AAATTTTCA CTTTAACTT TCAATTAATA TCAATGCTAT ATATCGGCTT TCACTATAT
33001	ATAACTTCC CGGCAGGTC ACTTAAGTTC ATGTGTCTGT CTAAATCTG AGCAGACAG TGTGTCTCTA TGTGTCTCTA CTTTAACTGAG GGTAAAGTA
33101	TATTTGAGG GCGGTCTGAG TGAATTCAG TACAGGACA GTTGTACGAC TCGTGTCTCG ACACAGGCTT GAACTGCTCC GAACTGCTCC GCGCTTCTCT
33201	AACTTCACCC CTACATGCG GTAGATTCAT ATGTGTCTAT CAGGATAGG CCGTGTGCTT GCAGAGGCTT GCGATTAAC TCGTGTCTCC GCGCTTCTCT
33301	TTACAGTCC GATGTACCC CATCTACATA TTACAGCTA TGTGTCTCTT GCGAGGCTT GCGAGGCTT GCGAGGCTT GCGAGGCTT GCGAGGCTT
33401	CCTGCAAGAA TACACATGCG CAGTGTCTCT CTGAGGATG GTACAGGAG GAGTGTCTCT TAAGCTGTCT TAAGCTGTCT TAAGCTGTCT TAAGCTGTCT
33501	CGACCTGCTT ATGTGTACG GTACAGGAG GAGTGTCTCT TAAGCTGTCT TAAGCTGTCT TAAGCTGTCT TAAGCTGTCT TAAGCTGTCT TAAGCTGTCT
33601	TCACATTAAT CAGCAGCTA ACTGAGGAC AGCAGGACA TATTTTTCNA ATTCGACAG TCGACAGGCT TGTATTCNA GCTCATGCG GGTACACAG
33701	AGTGAATTTA GTGTGTCTAT TGACGTCTTG TGTGTGTCTT ATACAAAGTT TTAGGCTGTC ACCTTCTCTG ACATAGGTTT CGGTACAGG CCGTGTCTCT
33801	AACCCAGTG GCGATCATAC CACAAGGCTA GGTAGATTAA GTTGTGACCC CTCATTAACA CTTGTGACAT AACATTAAC TCTTTTGGCA TGTGTTAAT
33901	TTGGGTGAC CCGTGTATG GTGTGTGCTT CCACTTAAT CAGGCTGCG GAGTATTTGT GCGACCTGTA TTGTAAATG AGAAACCTT ACACATTTA
34001	CAGCAGCTCC CCGTACCATTA TAAACCTCTG ATTAACATG GCGCCATCCA CCACTATCTT NAACAGCTT GCGCCGCGCT TATACACTT
34101	GTGTGTGAGG GCGATGTAT ATTTGTGAGC TAATTTGTAC CCGGTAGT GGTGTAGGA TTGTGTGAC TTGTGTGAC TTGTGTGAC TTGTGTGAC
34201	AGCGAACCG GACTGTAAAC ATGACAGTGT AGAGCCAGG ACTGTAAAC TCGATTAAC TCGATTAAC TCGATTAAC TCGATTAAC TCGATTAAC
34301	TCCTTTGCTT CTGACCTTGT TACTGTCTAC TCTCGGCTCC TCGCATTTG TCGCATTTG TCGCATTTG TCGCATTTG TCGCATTTG TCGCATTTG
34401	CTGTCTACCA CTCTCTCAG ATTACACCT CTTCCGCTT TACACCATTA TCGCAGGGA CAACCCATTC CTGATTAAC GTATATGCA CACTTCACT
34501	GACGTATGT GAGGAGTCC TATGTCTTCA GGAATGCTA ACTTTGTAT AGGTGCTT GTGTGTGAG GATTTAGTCT CATTATGCT GTATGCTCT
34601	AAGACCTCC AGTAACTCA CTTGTGCTAT TGTCAATCT TACATTAAC TACATTAAC TACATTAAC TACATTAAC TACATTAAC TACATTAAC
34701	TTCTGAGCG TCGATTTGAT GCAACATCA ACATTTTCA CATTGTGCTT TACTGTGCTT TACTGTGCTT TACTGTGCTT TACTGTGCTT TACTGTGCTT
34801	GAGGTGAGC GATCTTACT GTACGATTA CCGTGTGAG CCGTGTGAG CCGTGTGAG CCGTGTGAG CCGTGTGAG CCGTGTGAG CCGTGTGAG
34901	CCTCCATCTG CTAGGATGA CATCTCTAC GCGCTCTCT TCGCTCTAGC ACAACGACA TCGCATTTG TCGCATTTG TCGCATTTG TCGCATTTG

Figure 15U

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33601	CTGTAAGCAA ACCAGTGG GGGGTGACAA ACAATATTC GTCTTCGTC CAGAGCTTTA GATCCCTCTG TGTAGTAGTT GTATTATATC CACTCTCTTA
33701	GACTTCGT TTGTCCAGC CCGCAATCT TTCTTAGACG CAGAGCTTCAG AGTGGGCTCA TATACAGAC ACATATCAAA GATCATATAG GTGAGAGAT
33801	AAGCATCCAG GGGGGGGGCT GCTTCGAGTT CTATTATAC TGGCTTCCTC TATACAGAC CACCACCGCA GATTAAGCCA CACCCAGCC/
33901	TTCTGAGGTC CCGGGGGGAC CGAAGCCCA GATAGTATTC AGCAATAGC CCGGACGGG ACTATTATAG GTGGTGGCGT CTATTATCGGT GTGGCTCGAT
34001	ACCTACACAT TCGTCTCGG AGTCACACAC GGGAGAGTC GGAAGACCT GAAAGACCAT GTTTTTTTT TTATTCCTCAA AGATTATCCA AAKCTTANA
34101	TGGATCTGTA AGCAAGACCC TCAGTGTGTC CCGTCTCTCC CTTCTCTGAC CTTCTCTGTA CAAAGAAAAA AATAAGGTTT TCTAATAGCT TTTCGAGTTT
34201	ATGAGATCT ATTAACTGAA CCGGTCTCC TCGGTGGG TGTCTMACT CTACAGCAA AGAACAGATA ATGGCAATTT TAAGATGTTG CACATAGCT CACATAGCT
34301	TACTTCTAGA TAAATTCATT GGGGAGGCG AGGCCAGCC ACCAGTTTGA GATGTCTGTT TCTGTCTAT TACGGTAAAC ATTCTACAC GTTTTACCG/
34401	TCCAAAAGCC AAGGGGCGT CAGGTCCAG TGGAGTAA GGGTAATCC TTCAAGGTGA ATCTCTCTA TAAACATTC TAAACATTC AGCACCTTCA ACCATGCCA
34501	AGGTTTTCCG TTTCGGGGA GTGGAGGTC ACTCCATT CTCCATTCC CCAATCCCGA ATATTCCAG CCGGTAAAC TNGAGGAGAT ATTGTAAAG TGTGTAGGCT
34601	AATAATCTC ATCTCCAC CTCTCTATA TATCTTAAG TATCTTAAG ATATTCCAG CCGGTAAAC TNGAGGAGAT ATTGTAAAG TGTGTAGGCT CCGGTAAAC
34701	CAOCTCAG CAGCGAATCA TGAATGCAA AATTCAGTT CCTCAGAC CTGTATAAGA TTCAAAAGCG GAACATTAAC AAAAAATCCG CGATCCCTA
34801	GTGGAGTTC GTGCTTAGT ACTAACGTT TTAAGTCCAA GAGGTGCTG GACATATTT AGCTTTTCC AGCTTTTCC CTTGTAAATG TTTTATGCG CATNGGCAI
34901	GGTCCCTTC CAGGCCAGC TGAACTAAT COTTCAGTTC TGCAGGACC AGCGGGGA CAGGTGGCTA GAGGGGCGG TCGTTGCTAC TGTTTTCTG GGTGTGACTA
35001	CCAGGGAAC GTCCCGGTCG ACTTCTATTA GCAGTCCAG ACCTGCCG TCGCGCGGT GAGGGGCGG TCGTTGCTAC TGTTTTCTG TGTTTTCTG GGTGTGACTA
35101	TATGACACG ATACTCGAG CTATCTAAC CAGGTAGCC CCGATTAAG CTGTGTGAT GGGGGGCGT ATAAATGCA AGGTGCTCT CAANAATC/
35201	ATACTGTCCG TATGAGCTC GATACGATT GTGCAATCG GGTACATTC GACAAAGCTA CCGCGCGCTA TATTTTACGT TCCACAGCA GTTTTTCG/
35301	GGCAAGCT CCGGCAAAA AGAAGCACA TGTAGTCA TGTAGTCA GTTCATGCG ATAAAGCGG GTTAGGCGG GATTAAGAC AGCAATTTTC
35401	CGGTTTCGGA GCGGTTTTT TCTTCTGCT AGCATCAGTA CCGTACGTC TATTTCCGTC CATTCGAGG CTGTGCGTG TCTTTTCTG TCGTAAAG
35501	TCTCAACAT GTCTGCGGT TTCTGCATA ACACAAATA AATTAACAA AATTAACAA TGTGTAACT TGTGTAACT GGTGTAACT TGTGTAACT
35601	AGAGTTGTA CAGACGCCA AAGAGCTAT TGTGTTTTT TGTGTTTTT TGTGTTTTT TGTGTTTTT TGTGTTTTT TGTGTTTTT TGTGTTTTT
35701	ATAGCATTA GACGACTAC GCGCATGCC GCGTACGCC CCGTACGCC CCGTACGCC CCGTACGCC CCGTACGCC CCGTACGCC CCGTACGCC
35801	TCATATGTA AGACTCGTA MACATCAG GTTGATTCAC ATCGTCACT GCTAAMAGC GACCGAATA GACCGAATA GACCGAATA GACCGAATA
35901	AGTATTACAT TCTGAGCCAT TTGTGTAGTC CAACTAAGTC TAGCCAGTCA CCGTTTTTC GCTAAMAGC GACCGAATA GACCGAATA GACCGAATA
36001	AGACACAT TGTGAGGAT ATCTTCCATA TTCTTTTAT TTCTTTTAT TTCTTTTAT TTCTTTTAT TTCTTTTAT TTCTTTTAT TTCTTTTAT
36101	TCCGCTTCA GACACATA CAGGCTTC ACAGCGGAG CCAATACAGT CAGCTTAC CAGCTTAC CAGCTTAC CAGCTTAC CAGCTTAC
36201	AGGGGAGGT CTGTGTTAT GTGCGGAGG TGTGCGGTC GGTATGTCA GTGCGGAGG TGTGCGGTC GGTATGTCA GTGCGGAGG TGTGCGGTC
36301	GGCACAGCT CAATCAGTCA CAGGTANA AAGGCCAG AGGCCAGG TGTGCGGTC GGTATGTCA GTGCGGAGG TGTGCGGTC GGTATGTCA
36401	CCGTGGTGA GTTAGTCA GTACATTTT TCCCGGTC ACCTTCCGT CATATATAT CATATATAT CATATATAT CATATATAT CATATATAT CATATATAT
36501	CCAGAAAC CCGACGCGA CTTACGCCA CTAAGGCTT CTAAGGCTT CTAAGGCTT CTAAGGCTT CTAAGGCTT CTAAGGCTT CTAAGGCTT
36601	GGGTCTTTTG GGTGCGCTT GGTGCGCTT GGTGCGCTT GGTGCGCTT GGTGCGCTT GGTGCGCTT GGTGCGCTT GGTGCGCTT GGTGCGCTT

Figure 15V

pMRKarl59ag MER6R2

35301 CATTATTGCA AACTACAAAT TCCACACACA TACAGTTTAC TCCGCGCTTA AACTAGCTC ACCGCGCCCG TTCCGACGCG CCGCGCCACG TCCCAAACTC
GTAAATTTCT TTGATGTTA AGGCTTGCT ATGTTCAATG ACCGCTGAT TTGATGACG TTGACGCGCG AAGGCTGCGG GCGCGCGTGC AGTGTTTGAG

35401 CACCCCTCA TTATCATATT GCTTCAATC CAAATNAGG TATATTATG ATGATGTA TTANGATTC GATCTGCGA GCGTAGGCTG GATGCGCTT
GTGCGGAGT AATGATATTA CCGAATTTAG GTTTTATTCG TACTACAAAT TACTTTTAAG CCTAGACGCT GCGCTCCGAC CTACCGGAAAG

35501 CCGATTATGA TTCTCTGCG TTCCGCGGCG ATCGGATTC CCGGTTTCCA CCGCTAGGCG TAGATATGGA CAGCTTCAAG CAGCTTCAAG
CGTAAATCT AAGAGAGCG AAGCGCGCG TAGCCCTAG GCGGTAAGCT GCGCTAGGAC ATCTACTGCT GGTAGTCCCT GTGGAAGTTC

35601 GCGAGCAAA GCGCAGAAC GGTAAAGG GCGCTTCT GCGCTTCT CCGCTTCT CCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT
CGCTTCTT CCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

35701 GAGTGTGGA AACTGACAG GACTATAAG ATACCAGCG TTTCGCGCG TTTCGCGCG TTTCGCGCG TTTCGCGCG TTTCGCGCG TTTCGCGCG
CTCACCGCT TTGCGCTG CCGATATTTT TATGCTGCG TATGCTGCG TATGCTGCG TATGCTGCG TATGCTGCG TATGCTGCG

35801 TTCTCCGCT TTCTCCGCT GCGAGCGTG GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT
GACGCGCGA AAGAGCGAG CCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

35901 TCGACCAACC CCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT
ACGCTGCTG GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

36001 CACTGCTAC AGATTATGA GAGGAGGTA TGTAGCGCT GCTAGAGCT TCTTGAAGT GTGCGCTAC TACGCTACA CTAGAGGAG AGTATTTGCT
GTGACCAATG TCTTAATCT CTGCTGCT ATCTGCTA GATCTGCTA GATCTGCTA GATCTGCTA GATCTGCTA GATCTGCTA

36101 ATCTGCGCT TACTGAGCG AGTATCTT CCGAAGAGG TTGCTGCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT
TACGCGGAG AGCTTCTG TCAATGAG CCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

36201 AGCGGCGAT TACGCGGAG AAGAGGAT CTCAAGAG TCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT
TCTGCTGCTA ATGCGGCT TTCTTCTGTA GATCTGCTA GATCTGCTA GATCTGCTA GATCTGCTA GATCTGCTA GATCTGCTA

36301 TTGCTGCTA AGATTATGA AAGGATCT CACTAGAT CCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT
AAACGATAC TCTAATGAT TTCTGAGAA GTGCTGCTA GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

36401 TCACTGAGCG ACGATCTCA GCGATCTGCT TATTGCTGCT AATGAGGAG ATGAGGAG TACTGCTCA GCGCTTCT GCGCTTCT GCGCTTCT
AGTCACTCG TGTATGAT CCGTACAG CCGTACAG ATGAGGAG TACTGCTCA GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

36501 TCGCGCGCT GCTGCAATGA TACCGCGAG CCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT
ACCGCGCTA CCGCTTCT ATGCGCTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

36601 CCGCTTCT TATCGCTG CACTGCTG ATTAATGCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT
GAGCTTCTA ATAGCGGAG GTAGCTGAG TAATTAAGNA CCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

36701 CTACAGCAT CCGCTTCT CCGCTTCT TCGCTGCT TCGCTGCT TCGCTGCT TCGCTGCT TCGCTGCT TCGCTGCT TCGCTGCT
GATGCTGCTA GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

36801 AAGCGGCT ACGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT
TTCTGCGCA TCGAGGAG CAGGAGCT TCACTGAG TCACTGAG TCACTGAG TCACTGAG TCACTGAG TCACTGAG

36901 GTCATGCGAT CCGTATGAG CTCTTCTGCT ACTGCTGCT ACTGCTGCT ACTGCTGCT ACTGCTGCT ACTGCTGCT ACTGCTGCT ACTGCTGCT
CAGTACGCTA GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT GCGCTTCT

Figure 15W

pMRAd5qag MERG82

37001 CACACGGGA TANTACCGG CCACATACCA GACTTTTAA AGT ATCATE ATTGAAAC GTCTTCGG GCGAAACTC TCACGACTC TACTCTCTTT
 GTTGTCCCT ATTATGGCGG GGTGTATCGT CTTCGAATTT TCA GACTAG TACCTTTTG CAAGAGGCC CCTTTTGAG AGTTCTTAGA ATGCGACAA
 37101 GAGATCCAGT TCGATTGAC CCACTCTGGC ACTCAATCCA TCTTAAATAT TCTTACTTT CACCTGCTT TCTGGGTGAG GAAACACAGC AGCGCAANT
 CTCAGGTCAG AGCTACATTG GTTCAGCAGC TCGGTGACT AGAATCTATA GAAATGAAA GTCTGTCCA AGACCCACTC GTTTTGTCC TTCCCTTTTA
 37201 GCGCGAATAA AGGGAATAAG GCGGACACCG AATGTTTGA TACTATAGT CTTCCTTTT CAATATATT GAGCATTTA TCAGGTATAT TCTCTCATCA
 CCGCGTTTTT TCCCTTATTC CCGCTGTGCC TTACAACTT ATCAATATCA GAGCAAAA GTTATATAA CTTCGTAAAT AGTCCCAATA ACAGAGTAT
 37301 GCGGATACAT ATTGCAATGT ATTAGAAA ATAAACAAAT AGGATTTCC CCAACATTC CCGCAAGT GCCACCTGAG GTCTAAGAAA CCATTATTA
 CCGCTATGTA TAACTTACA TAAATCTTTT TATTGTITA TCCCAAGGC GCGGTAAAG GCGCTTTCA CCGTGGACTG CAGNTCTTT GGTAAATAATA

EcoRI
 BamHI
 HindIII

37401 CATGACATTA ACCTATAAA ATAGCGTAT CACGAGGCC TTTCGTCTTC AGCAATTGGA TCGCATTTCT TAAT (SEQ ID NO: 27)
 GTACTGTAAAT TGGATATTTT TATCCGATA GTGCTCGGG AAGCAGAG AGTTCTTAAGCT AGCCTTAAGA ATTA (SEQ ID NO: 28)

Figure 15X

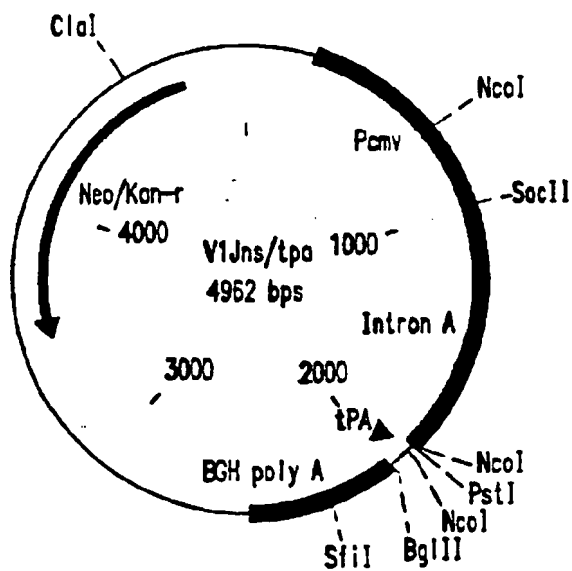
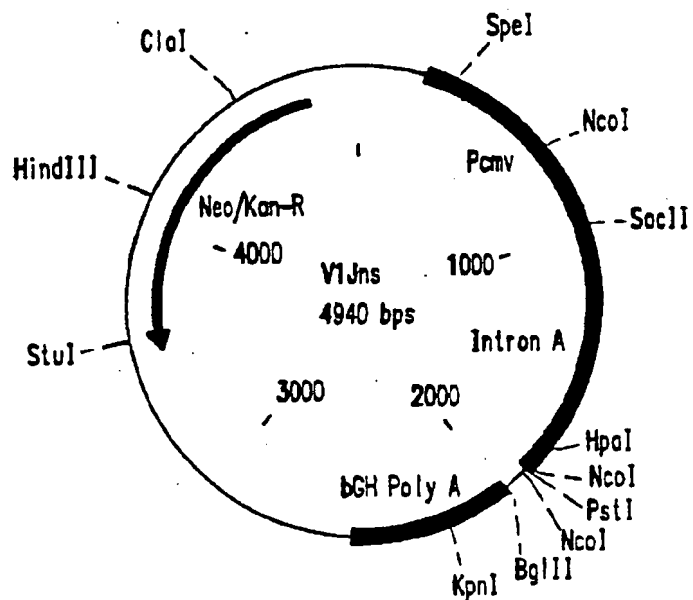


FIGURE 16

AGATCTACCATGGCCCCATCTCCCCATTGAGACTGTCCCTGTGAAGCTGAAGCCTGGCATGGATGGCCCCAAGGTGAA
 Bg/II MetAlaProIleSerProIleGluThrValProValLysLeuLysProGlyMetAspGlyProLysValLy
 1 10 20
 GCAGTGGCCCCGTGACTGAGGAGAAGATCAAGGCCCTGGTGGAAATCTGCACTGAGATGGAGAAGGAGGGCAAAATCTCCA
 sGlnTrpProLeuThrGluGluLysIleLysAlaLeuValGluIleCysThrGluMetGluLysGluGlyLysIleSerL
 30 40 50
 AGATTGGCCCCGAGAACCCCTACAACACCCCTGTGTTTGCATCAAGAAGAAGGACTCCACCAAGTGGAGGAACCTGGTG
 ysIleGlyProGluAsnProTyrAsnThrProValPheAlaIleLysLysLysAspSerThrLysTrpArgLysLeuVal
 60 70
 GACTTCAGGAGCTGAACAAGAGGACCCAGGACTTCTGGGAGGTGCAGCTGGGCATCCCCACCCCGCTGGCCTGAAGAA
 AspPheArgGluLeuAsnLysArgThrGlnAspPheTrpGluValGlnLeuGlyIleProHisProAlaGlyLeuLysLy
 80 90 100
 GAAGAAGTCTGTGACTGTGCTGGCTGTGGGGATGCCTACTTCTGTGCCCCCTGGATGAGGACTTCAGGAAGTACACTG
 sLysLysSerValThrValLeuAlaValGlyAspAlaTyrPheSerValProLeuAspGluAspPheArgLysTyrThrA
 110 120 130
 CCTTCACCATCCCCCTCCATCAACAATGAGACCCCTGGCATCAGGTACCAGTACAATGTGCTGCCCCAGGGCTGGAAGGGC
 loPheTnrIleProSerIleAsnAsnGluThrProGlyIleArgTyrGlnTyrAsnValLeuProGlnGlyTrpLysGly
 140 150
 TCCCCGCCATCTTCCAGTCCCTCCATGACCAAGATCCTGGAGCCCTTCAGGAAGCAGAACCCTGACATTGTGATCTACCA
 SerProAlaIlePheGlnSerSerMetThrLysIleLeuGluProPheArgLysGlnAsnProAspIleValIleTyrGl
 160 170 180
 GTACATGGCTGCCCTGTATGTGGGCTCTGACCTGGAGATTGGGCAGCACAGGACCAAGATTGAGGAGCTGAGGCAGCACC
 nTyrMetAlaAlaLeuTyrValGlySerAspLeuGluIleGlyGlnHisArgThrLysIleGluGluLeuArgGlnHisL
 190 200 210
 TGCTGAGGTGGGGCTGACCACCCCTGACAAGAAGCACCAGAAGGAGCCCCCTTCCTGTGGATGGGCTATGAGCTGCAC
 euLeuArgTrpGlyLeuThrThrProAspLysLysHisGlnLysGluProProPheLeuTrpMetGlyTyrGluLeuHis
 220 230
 CCGACAACTGGACTGTGCAGCCCATTTGTGCTGCCTGACAAGGACTCCTGGACTGTGAATGACATCCAGAAGCTGGTGGG
 ProAspLysTrpThrValGlnProIleValLeuProGluLysAspSerTrpThrValAsnAspIleGlnLysLeuValGl
 240 250 260
 CAAGCTGAAGTGGGCCTCCCAAATCTACCCCTGGCATCAAGGTGAGGCAGCTGTGCAACCTGCTGAGGGGCACCAAGGCC
 yLysLeuAsnTrpAlaSerGlnIleTyrProGlyIleLysValArgGlnLeuCysLysLeuLeuArgGlyThrLysAlaL
 270 280 290

FIGURE 17A

TGACTGAGCTGATCCCCCTGACTGAGGAGGCTGAGCTGGAGCTGGCTGAGAACAGGAGATCCTGAAGGAGCCTGTGCAT
 EuThrGluVolIleProLeuThrGluGluAlaGluLeuGluLeuAlaGluAsnArgGluIleLeuLysGluProValHis
 300 310

GGGGTGTACTATGACCCCTCCAAGGACCTGATTGCTGAGATCCAGAAGCAGGGCCAGGGCCAGTGGACCTACCAAATCTA
 GlyVolTyrTyrAspProSerLysAspLeuIleAlaGluIleGlnLysGlnGlyGlnGlyGlnTrpThrTyrGlnIleTy
 320 330 340

CCAGGAGCCCTTCAAGAACCTGAAGACTGGCAAGTATGCCAGGATGAGGGGGGGCCACACCAATGATGTGAAGCAGCTGA
 rGlnGluProPheLysAsnLeuLysThrGlyLysTyrAlaArgMetArgGlyAlaHisThrAsnAspValLysGlnLeuT
 350 360 370

CTCAGGCTGTGCAGAAGATCACCCTGAGTCCATTGTGATCTGGGCAACACCCCAAGTTCAAGCTGCCCATCCAGAAG
 hrGluAlaVolGlnLysIleThrThrGluSerIleValIleTrpGlyLysThrProLysPheLysLeuProIleGlnLys
 380 390

GAGACCTGGGAGACCTGGTGGACTGAGTACTGGCAGGCCACCTGGATCCCTGAGTGGGAGTTTGTGAACACCCCCCCT
 GluThrTrpGluThrTrpTrpThrGluTyrTrpGlnAlaThrTrpIleProGluTrpGluPheValAsnThrProProLe
 400 410 420

GGTCAAGCTGTGGTACCAGCTGGAGAAGGAGCCCATTTGTGGGGCTGAGACCTTCTATGTGGCTGGGGCTGCCAACAGGG
 uVolLysLeuTrpTyrGlnLeuGluLysGluProIleValGlyAlaGluThrPheTyrValAlaGlyAlaAlaAsnArgG
 430 440 450

AGACCAAGCTGGGCAAGGCTGGCTATGTGACCAACAGGGCAGGCAGAGGTTGGTGACCTGACTGACACCACCAACCAG
 luThrLysLeuGlyLysAlaGlyTyrValThrAsnArgGlyArgGlnLysValValThrLeuThrAspThrThrAsnGln
 460 470

AAGACTGCCCTCCAGGCCATCTACCTGGCCCTCCAGGACTCTGGCCTGGAGGTGAACATTGTGACTGCCCTCCAGTATGC
 LysThrAlaLeuGlnAlaIleTyrLeuAlaLeuGlnAspSerGlyLeuGluValAsnIleValThrAlaSerGlnTyrAl
 480 490 500

CCTGGGCATCATCCAGGCCAGCCTGATCAGTCTGAGTCTGAGCTGGTGAACCAGATCATTGAGCAGCTGATCAAGAAGG
 aLeuGlyIleIleGlnAlaGlnProAspGlnSerGluSerGluLeuValAsnGlnIleIleGluGlnLeuIleLysLysG
 510 520 530

AGAAGGTGTACCTGGCCTGGTGCCTGCCACAAGGCCATTGGGGCAATGAGCAGGTGGACAAGCTGGTGTCTGCTGGC
 luLysValTyrLeuAlaTrpValProAlaHisLysGlyIleGlyGlyAsnGluGlnValAspLysLeuValSerAlaGly
 540 550

ATCAGGAAGGTGCTGTTCTGGATGGCATTGACAAGGCCCAGGATGAGCATGAGAAGTACCACTCCAAGTGGAGGGCTAT
 lleArgLysValLeuPheLeuAspGlyIleAspLysAlaGlnAspGluHisGluLysTyrHisSerAsnTrpArgAlaMe
 560 570 580

FIGURE 17B

GGCCTCTGACTTCAACCTGCCCCCTGTGGTGGCTAAGGAGATTGTGGCTCCTGTGACAAGTCCCAGCTGAAGGGGAGG
 tAlaSerAspPheAsnLeuProProValValAlaLysGluIleValAlaSerCysAspLysCysGlnLeuLysGlyGluA
 590 600 610

CCATGCATGGGAGGTGGACTGCTCCCTGGCATCTGGCAGCTGGCTGCACCCACCTGGAGGGCAAGGTGATCCTGGTG
 lAlaMetHisGlyGlnValAspCysSerProGlyIleTrpGlnLeuAlaCysThrHisLeuGluGlyLysValIleLeuVal
 620 630

GCTGTGCATGTGGCTCCGGCTACATTGAGGCTGAGGTGATCCCTGCTGAGACAGGCCAGGAGACTGCCTACTTCCTGCT
 AlaValHisValAlaSerGlyTyrIleGluAlaGluValIleProAlaGluThrGlyGlnGluThrAlaTyrPheLeuLe
 640 650 660

GAAGCTGGCTGGCAGGTGGCTGTGAAGACCATCCACACTGCCAATGGCTCCAATTCACTGGGGCCACAGTGAGGGCTG
 uLysLeuAlaGlyArgTrpProValLysThrIleHisThrAlaAsnGlySerAsnPheThrGlyAlaThrValArgAlaA
 670 680 690

CCTGCTGGTGGCTGGCATCAAGCAGGAGTTTGGCATCCCCTACAACCCCACTCCAGGGGGTGGTGGCTCCATGAAC
 lAlaCysTrpTrpAlaGlyIleLysGlnGluPheGlyIleProTyrAsnProGlnSerGlnGlyValValAlaSerMetAsn
 700 710

AAGGAGCTGAAGAAGATCATTGGGCAGGTGAGGGACCAGGCTGAGCACCTGAAGACAGCTGTGCAGATGGCTGTGTTCAT
 LysGluLeuLysLysIleIleGlyGlnValArgAspGlnAlaGluHisLeuLysThrAlaValGlnMetAlaValPheIle
 720 730 740

CCACAACCTCAAGAGGAAGGGGGCATCGGGGGCTACTCCGCTGGGGAGAGGATTGTGGACATCATGCCACAGACATCC
 eHisAsnPheLysArgLysGlyGlyIleGlyGlyTyrSerAlaGlyGluArgIleValAspIleIleAlaThrAspIleG
 750 760 770

AGACCAAGGAGCTCCAGAAGCAGATCACCAGATCCAGAACTTCAGGGTGTACTACAGGGACTCCAGGAADCCCTGTGG
 lThrLysGluLeuGlnLysGlnIleThrLysIleGlnAsnPheArgValTyrTyrArgAspSerArgAsnProLeuTrp
 780 790

AAGGGCCCTGCCAAGCTGCTGTGAAGGGGGAGGGGGCTGTGGTGATCCAGGACAACCTGACATCAAGGTGGTGGCCAG
 LysGlyProAlaLysLeuLeuTrpLysGlyGluGlyAlaValValIleGlnAspAsnSerAspIleLysValValProAr
 800 810 820

GAGGAAGGCCAAGATCATCAGGGACTATGCCAAGCAGATGGCTGGGGATGACTGTGTGGCTCCAGGCAGGATGAGGACT
 gArgLysAlaLysIleIleArgAspTyrGlyLysGlnMetAlaGlyAspAspCysValAlaSerArgGlnAspGluAspx
 830 840 850

AAAGCCCGGGCAGATC (SEQ ID NO: 3)
 Xx Bg11 (SEQ ID NO: 4)

FIGURE 17C

FIGURE 18

WT	- ATG GGT GGC AAG TGG TCA AAA CGT AGT GTG CCT GGA TGG TCT	-42
OPT	- ATG GGC GGC AAG TGG TCC AAG AGG TCC GTG CCC GGC TGG TCC M G G K W S K R S V P G W S	-14
WT	- ACT GTA AGG GAA AGA ATG AGA CGA GCT GAG CCA GCA GCA GAT	-84
OPT	- ACC GTG AGG GAG AGG ATG AGG AGG GCC GAG CCC GCC GCC GAC T V R E R M R R A E P A A D	-28
WT	- AGG GTG AGA CGA ACT GAG CCA GCA GCA GTA GGG GTG GGA GCA	-126
OPT	- AGG GTG AGG AGG ACC GAG CCC GCC GCC GTG GGC GTG GGC GCC R V R R T E P A A V G V G A	-42
WT	- GTA TCT CGA GAC CTG GAA AAA CAT GGA GCA ATC ACA AGT AGC	-168
OPT	- GTG TCC AGG GAC CTG GAG AAG CAC GGC GCC ATC ACC TCC TCC V S R D L E K H G A I T S S	-56
WT	- AAT ACA GCA GCT ACC AAT GCT GAT TGT GCC TGG CTA GAA GCA	-210
OPT	- AAC ACC GCC GCC ACC AAC GCC GAC TGC GCC TGG CTG GAG GCC N T A A T N A D C A W L E A	-70
WT	- CAA GAG GAT GAG GAA GTG GGT TTT CCA GTC AGA CCT CAG GTA	-252
OPT	- CAG GAG GAC GAG GAG GTG GGC TTC CCC GTG AGG CCC CAG GTG Q E D E E V G F P V R P Q V	-84
WT	- CCT TTA AGA CCA ATG ACT TAC AAG GGA GCT GTA GAT CTT AGC	-294
OPT	- CCC CTG AGG CCC ATG ACC TAC AAG GGC GCC GTG GAC CTG TCC P L R P M T Y K G A V D L S	-98
WT	- CAC TTT TTA AAA GAA AAG GGG GGA CTG GAA GGG CTA ATT CAC	-336
OPT	- CAC TTC CTG AAG GAG AAG GGC GGC CTG GAG GGC CTG ATC CAC H F L K E K G G L E G L I H	-112
WT	- TCA CAG AAA AGA CAA GAT ATC CTT GAT CTG TGG GTC TAC CAC	-378
OPT	- TCC CAG AAG AGG CAG GAC ATC CTG GAC CTG TGG GTG TAC CAC S Q K R Q D I L D L W V Y H	-126
WT	- ACA CAA GGC TAC TTC CCT GAT TGG CAG AAC TAC ACA CCA GGG	-420
OPT	- ACC CAG GGC TAC TTC CCC GAC TGG CAG AAC TAC ACC CCC GGC T Q G Y F P D W D N Y T P G	-140

FIGURE 19A

WT	- CCA GGA ATC AGA TTT CCA TTG ACC TTT GGA TGG TGC TTC AAG	-462
OPT	- CCC GGC ATC AGG TTC CCC CTG ACC TTC GGC TGG TGC TTC AAG	
	P G I R F P L T F G W C F K	-154
WT	- CTA GTA CCA GTT GAG CCA GAA AAG GTA GAA GAG GCC AAT GAA	-504
OPT	- CTG GTG CCC GTG GAG CCC GAG AAG GTG GAG GAG GCC AAC GAG	
	L V P V E P E K V E E A N E	-168
WT	- GGA GAG AAC AAC TGC TTG TTA CAC CCT ATG AGC CAG CAT GGG	-546
OPT	- GGC GAG AAC AAC TGC CTG CTG CAC CCC ATG TCC CAG CAC GGC	
	G E N N C L L H P M S Q H G	-182
WT	- ATA GAG GAC CCG GAG AAG GAA GTG TTA GAG TGG AGG TTT GAC	-588
OPT	- ATC GAG GAC CCC GAG AAG GAG GTG CTG GAG TGG AGG TTC GAC	
	I E D P E K E V L E W R F D	-196
WT	- AGC AAG CTA GCA TTT CAT CAC GTG GCC CGA GAG CTG CAT CCG	-630
OPT	- TCC AAG CTG GCC TTC CAC CAC GTG GCC AGG GAG CTG CAC CCC	
	S K L A F H H V A R E L H P	-210
WT	- GAG TAC TAC AAG GAC TGC TGA (SEQ ID NO:30)	-651
OPT	- GAG TAC TAC AAG GAC TGC TAA (contained within SEQ ID NO:9)	
	E Y Y K D C (SEQ ID NO:10)	-216

FIGURE 19B

V1Jns/nef *PstI* *BglII*
 CATGGGTCCTTTCTGCAAGTCACCGTCCTTGAGATCTGCCACC ATG GGC GGC AAG TGG TCC MAG AGG TCC GTG CCC
 M G G K K W S K R S V P
 CAC CCC GAG TAC TAC AAG GAC TGC TAA AGCCCGGACAGATCTGCTGTGCTCTCTAGTTGCCAGC (SEQ ID NO: 38)
 H P E Y Y K D C * (contained within SEQ ID NO:10)
 V1Jns/nef(G2A,LLAA)
 CATGGGTCCTTTCTGCAAGTCACCGTCCTTGAGATCTGCCACC ATG GGC GGC AAG TGG TCC AAG AGG TCC GTG CCC
 M A G K K W S K R S V P
 CAC CCC GAG TAC TAC AAG GAC TGC TAA AGCCCGGACAGATCTGCTGTGCTCTCTAGTTGCCAGC (SEQ ID NO: 39)
 H P E Y Y K D C * (contained within SEQ ID NO:14)
 V1Jns/tpanef & V1Jns/tpanef(LLAA)
 CATGGGTCCTTTCTGCAAGTCACCGTCCTTTATCTAGATCACC ATG GAT GCA ATG MAG AGA GGG CTC TGC TGT GTG
 M D A M K R G L C C V
 CTG CTG TGT GGA GCA GTC TTC GTT TCG CCC AGC GAG ALC ICC TCC MAG AGG TCC GTG CCC
 L L L C G A V F V S P S E I S S K R S V P
 CAC CCC GAG TAC TAC AAG GAC TGC TAA AGCCCGGACAGATCTGCTGTGCTCTCTAGTTGCCAGC (SEQ ID NO: 40)
 H P E Y Y K D C * (contained within SEQ ID NO: 16)

FIGURE 20

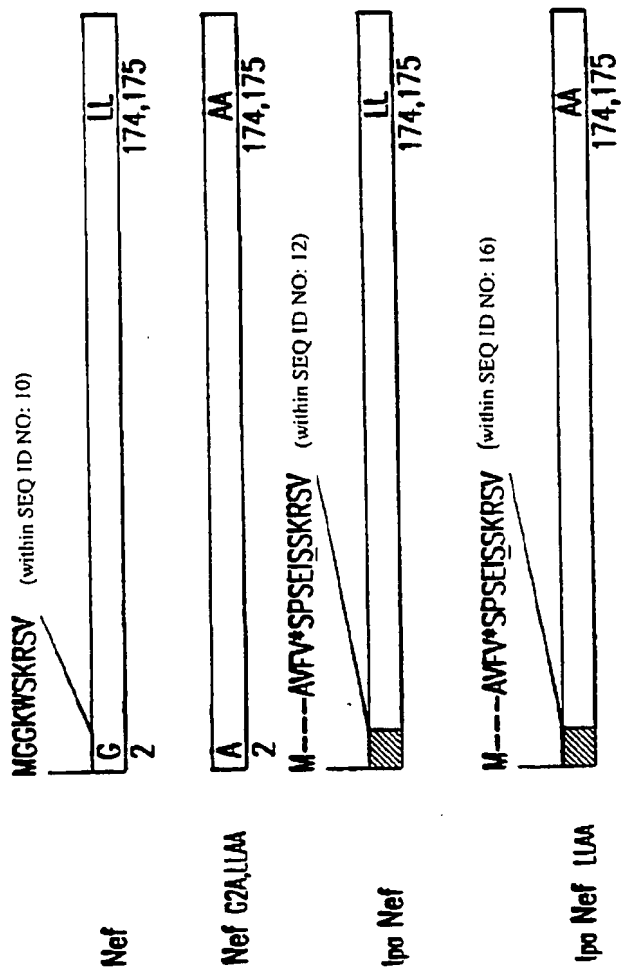


FIGURE 21

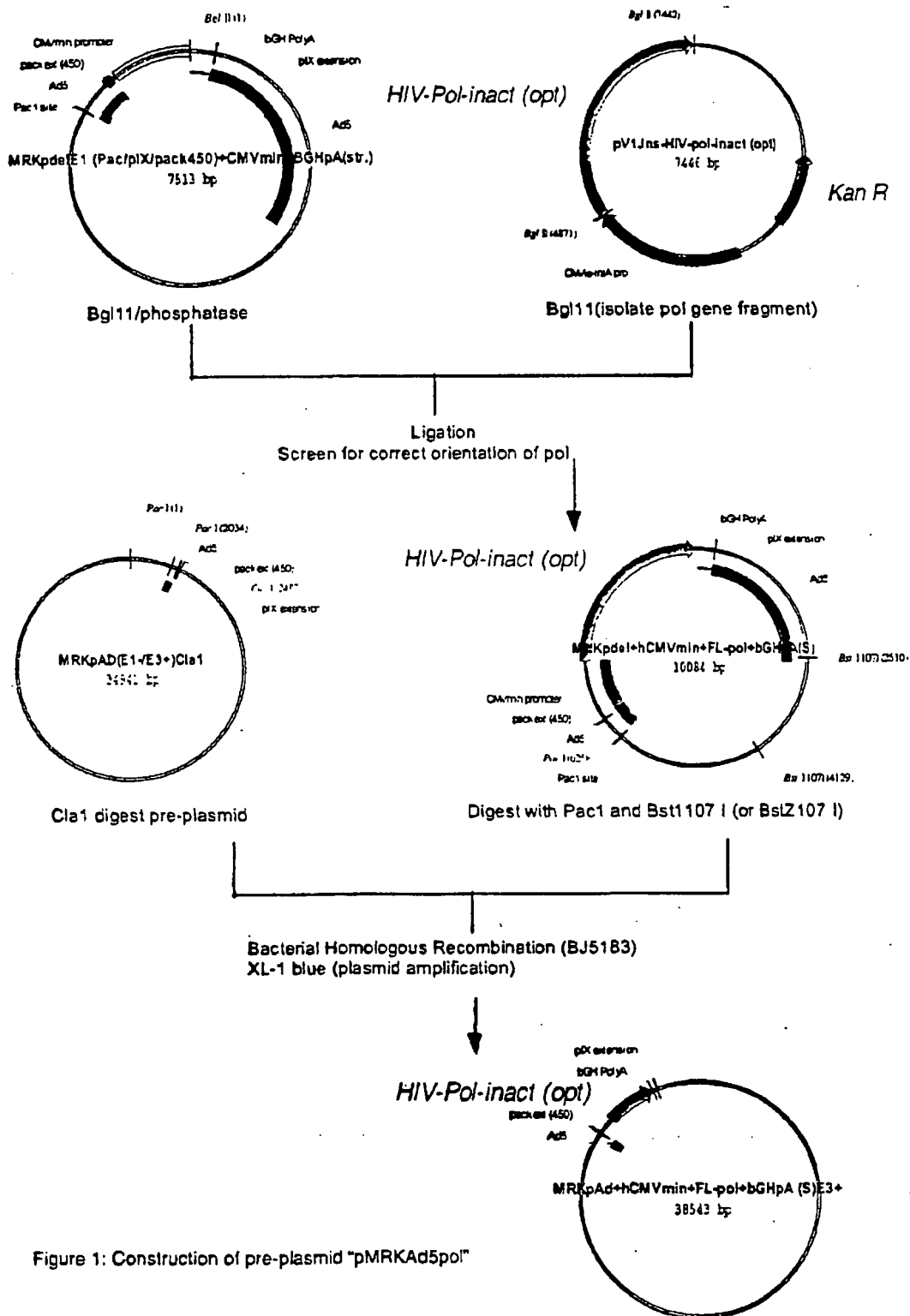


Figure 1: Construction of pre-plasmid "pMRKAd5pol"

FIGURE 22

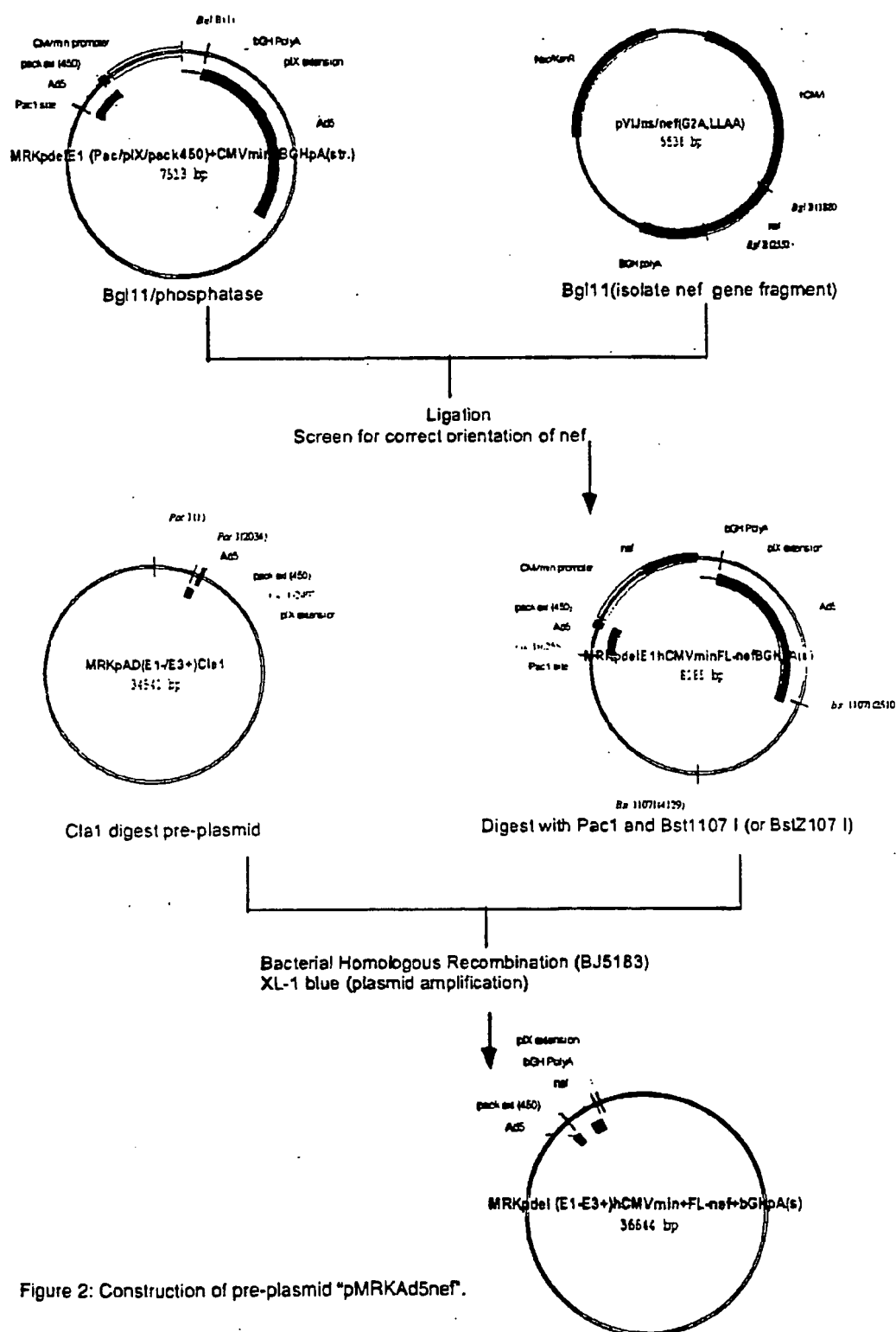
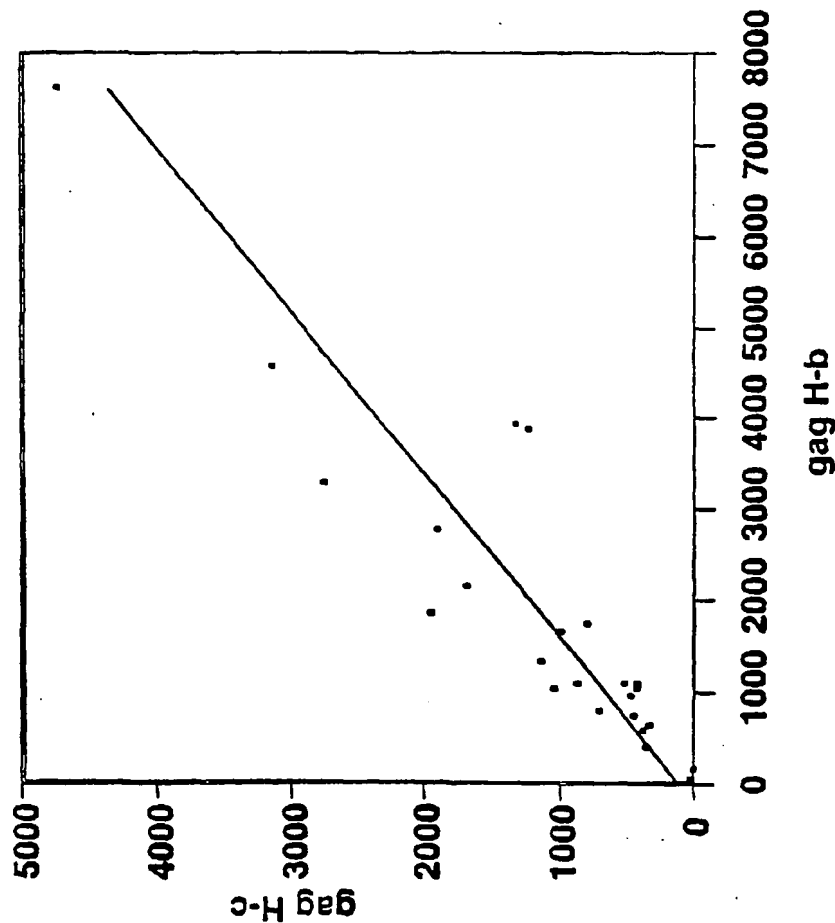


Figure 2: Construction of pre-plasmid "pMRKAd5nef".

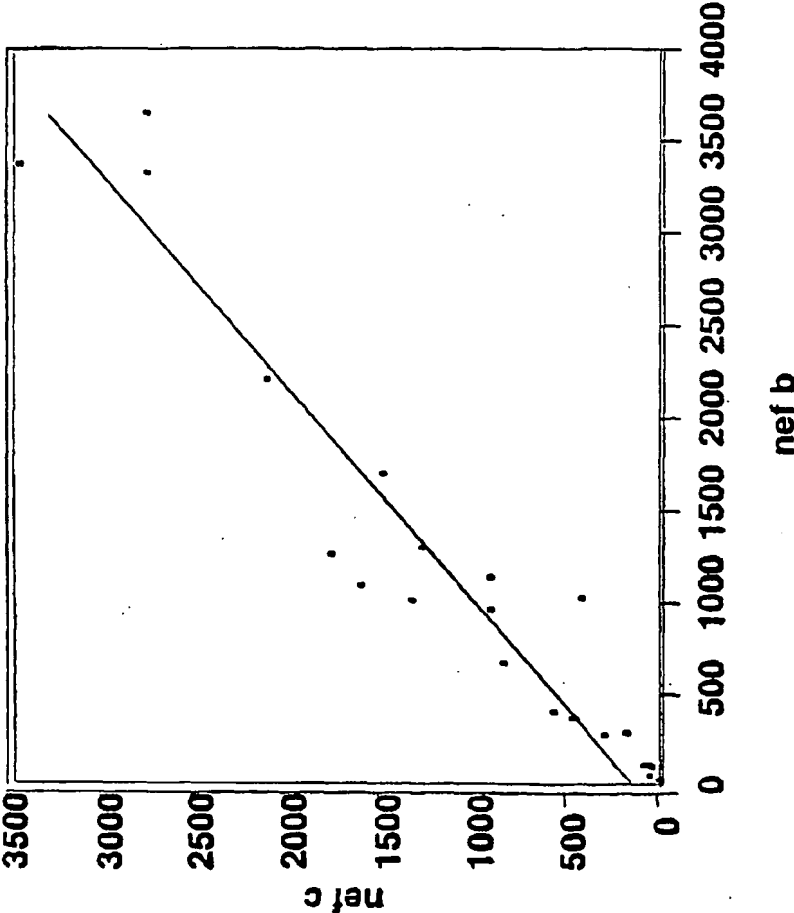
FIGURE 23

Comparison of Clade B vs. Clade C Anti-gag T Cell Responses in Clade B HIV-Infected Subjects



Linear Fit	
gag H-c = 111.603 + 0.55866 gag H-b	
Summary of Fit	
RSquare	0.816775
RSquare Adj	0.80914
Root Mean Square Error	474.9639
Mean of Response	1158.115
Observations (or Sum Wgts)	26

Comparison of Clade B vs. Clade C Anti-nef T Cell Responses in Clade B HIV-Infected Subjects



nef c = 131.132 + 0.8646 nef b

Summary of Fit	
RSquare	0.91685
RSquare Adj	0.91289
Root Mean Square Error	289.7718
Mean of Response	1096.435
Observations (or Sum Wgts)	23

FIGURE 25

MRKAd5pol MER1062
(MRKAd5 Pre-Adenoviral Vector Containing the IA opt pol Coding Region)

```

1  CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG
   GTAGTAGTTA TTATATGGAA TAAACCTAA CTCGGTTAT ACTATTACTC

51  GGGGTGGAGT TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG
   CCCACCTCA AACACTGCAC CGCGCCCCGC ACCCTTGCCC CGCCCACTGC

101 TAGTAGTGTG GCGGAAGTGT GATGTTGCAA GTGTGGCGGA ACACATGTAA
   ATCATCACAC CGCCTTCACA CTACAACGTT CACACCGCCT TGTGTACATT

151 GCGACGGATG TGGCAAAAGT GACGTTTTTG GTGTGCGCCG GTGTACACAG
   CGCTGCCCTAC ACCGTTTTCA CTGCAAAAAC CACACGCGGC CACATGTGTC

201 GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG TAAATTTGGG
   CTTCACTGTT AAAAGCGCGC CAAATCCGC CTACAACATC ATTTAAACCC

251 CGTAACCGAG TAAGATTGG CCATTTTCGC GGGAAACTG AATAAGAGGA
   GCATTGGCTC ATTCTAAACC GGTAAAAGCG CCCTTTTGAC TTATTCTCCT

301 AGTGAAATCT GAATAATTTT GTGTTACTCA TAGCGCGTAA TATTTGTCTA
   TCACTTTAGA CTTATTAAAA CACAATGAGT ATCGCGCATT ATAAACAGAT

351 GGGCCGCGGG GACTTTGACC GTTTACGTGG AGACTCGCCC AGGTGTTTTT
   CCCGGCGCCC CTGAAACTGG CAAATGCACC TCTGAGCGGG TCCACAAAAA

401 CTCAGGTGTT TTCCGCGTTC CGGGTCAAAG TTGGCGTTTT ATTATTATAG
   GAGTCCACAA AAGGCACAAG GCCCAGTTTC AACCGCAAAA TAATAATATC

451 GCGGCCGCGA TCCATTGCAT ACGTTGTATC CATATCATAA TATGTACATT
   CGCCGGCGCT AGGTAACGTA TGCAACATAG GTATAGTATT ATACATGTAA

501 TATATTGGCT CATGTCCAAC ATTACCGCCA TGTTGACATT GATTATTGAC
   ATATAACCGA GTACAGGTTG TAATGGCGGT ACAACTGTAA CTAATAACTG

551 TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA
   ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT

601 TGGAGTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG
   ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC

651 CCCAACGACC CCCGCCCAT TACGTCAATA ATGACGTATG TTCCCATAGT
   GGGTTGCTGG GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA

701 AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT
   TTGCGGTTAT CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

751 AAACTGCCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTACGCCC
   TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCATGCGGG

801 CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCCCAGTA
   GGATAACTGC AGTTACTGCC ATTTACGGG CGGACCGTAA TACGGGTCAT

851 CATGACCTTA TGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA
   GTACTGGAAT ACCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT

```

Figure 24A

901 TCGCTATTAC C GGTGATG CGGTTTGGC AGTACATCAA TGGGCG EA
 AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

 951 TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA
 ATCGCCAAAC TGAGTGCCCC TAAAGGTCA GAGGTGGGT AACTGCAGTT

 1001 TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA
 ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

 1051 ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG
 TGTGAGGCG GGGTAACGTC GTTACCCGC CATCCGCACA TGCCACCCTC

 1101 GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
 CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

 1151 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC
 GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTCGG

 1201 TCCGCGGCCG GGAACGGTGC ATTGGAACGC GGATTCCCCG TGCCAAGAGT
 AGCGCGCCGC CTTGCCACG TAACCTTGCG CTAAGGGGC ACGGTTCTCA

 1251 GAGATCTACC ATGGCCCCCA TCTCCCCAT TGAGACTGTG CCTGTGAAGC
 CTCTAGATGG TACCGGGGGT AGAGGGGGTA ACTCTGACAC GGACACTTCG

 1301 TGAAGCCTGG CATGGATGGC CCAAGGTGA AGCAGTGGCC CCTGACTGAG
 ACTTCGGACC GTACCTACCG GGGTCCACT TCGTCACCGG GGACTGACTC

 1351 GAGAAGATCA AGGCCCTGGT GGAAATCTGC ACTGAGATGG AGAAGGAGGG
 CTCCTCTAGT TCCGGGACCA CCTTTAGACG TGA CTCTACC TCTTCCTCCC

 1401 CAAAATCTCC AAGATTGGCC CCGAGAACCC CTACAACACC CCTGTGTTTG
 GTTTTAGAGG TTCTAACCGG GGCTCTGGG GATGTTGTGG GGACACAAAC

 1451 CCATCAAGAA GAAGGACTCC ACCAAGTGGA GGAAGCTGGT GGACTTCAGG
 GGTAGTTCTT CTTCTGAGG TGGTTCACCT CCTTCGACCA CCTGAAGTCC

 1501 GAGCTGAACA AGAGGACCCA GGACTTCTGG GAGGTGCAGC TGGGCATCCC
 CTCGACTTGT TCTCCTGGGT CCTGAAGACC CTCCACGTCG ACCCGTAGGG

 1551 CCACCCCGCT GGCCTGAAGA AGAAGAAGTC TGTGACTGTG CTGGCTGTGG
 GGTGGGGCGA CCGGACTTCT TCTTCTTCAG AACTGACAC GACCGACACC

 1601 GGGATGCCTA CTTCTCTGTG CCCCTGGATG AGGACTTCAG GAAGTACACT
 CCCTACGGAT GAAGAGACAC GGGGACCTAC TCCTGAAGTC CTTTATGTGA

 1651 GCCTTCACCA TCCCCTCCAT CAACAATGAG ACCCCTGGCA TCAGGTACCA
 CGGAAGTGGT AGGGGAGGTA GTTGTACTC TGGGGACCGT AGTCCATGCT

 1701 GTACAATGTG CTGCCCCAGG GCTGGAAGGG CTCCCCTGCC ATCTTCCAGT
 CATGTTACAC GACGGGGTCC CGACCTTCCC GAGGGGACGG TAGAAGGTCA

 1751 CCTCCATGAC CAAGATCCTG GAGCCCTTCA GGAAGCAGAA CCCTGACATT
 GGAGGTACTG GTTCTAGGAC CTCGGGAAGT CCTTCGTCTT GGGACTGTAA

 1801 GTGATCTACC AGTACATGGC TGCCCTGTAT GTGGGCTCTG ACCTGGAGAT
 CACTAGATGG TCATGTACCG ACGGGACATA CACCCGAGAC TGGACCTCTA

Figure 26B

1851 TGGGCAGCAC A CCAAGA TTGAGGAGCT GAGGCAGCAC CTGCTG T
 ACCCGTCGTG TCCTGGTTCT AACTCCTCGA CTCCGTCGTG GACGACTCA
 1901 GGGGCCTGAC CACCCCTGAC AAGAAGCACC AGAAGGAGCC CCCCTTCCTG
 CCCCGGACTG GTGGGGACTG TTCTTCGTGG TCTTCCTCGG GGGGAAGGAC
 1951 TGGATGGGCT ATGAGCTGCA CCCCAGACAAG TGGACTGTGC AGCCCATTTGT
 ACCTACCCGA TACTCGACGT GGGGCTGTTT ACCTGACACG TCGGGTAACA
 2001 GCTGCCTGAG AAGGACTCCT GGA CTGTGAA TGACATCCAG AAGCTGGTGG
 CGACGGACTC TTCCTGAGGA CCTGACACTT ACTGTAGGTC TTCGACCACC
 2051 GCAAGCTGAA CTGGGCCTCC CAAATCTACC CTGGCATCAA GGTGAGGCAG
 CGTTCGACTT GACCCGGAGG GTTTAGATGG GACCGTAGTT CCACTCCGTC
 2101 CTGTGCAAGC TGCTGAGGGG CACCAAGGCC CTGACTGAGG TGATCCCCCT
 GACACGTTTG ACGACTCCCC GTGGTTCCGG GACTGACTCC ACTAGGGGGA
 2151 GACTGAGGAG GCTGAGCTGG AGCTGGCTGA GAACAGGGAG ATCCTGAAGG
 CTGACTCCTC CGACTCGACC TCGACCGACT CTTGTCCCTC TAGGACTTCC
 2201 AGCCTGTGCA TGGGGTGTAC TATGACCCCT CCAAGGACCT GATTGCTGAG
 TCGGACACGT ACCCCACATG ATACTGGGGA GGTTCCTGGA CTAACGACTC
 2251 ATCCAGAAGC AGGGCCAGGG CCAGTGGACC TACCAAATCT ACCAGGAGCC
 TAGGTCTTCG TCCCGGTCCC GGTCACCTGG ATGGTTAGA TGGTCTTCGG
 2301 CTTCAAGAAC CTGAAGACTG GCAAGTATGC CAGGATGAGG GGGGCCCCACA
 GAAGTTCTTG GACTTCTGAC CGTTCATACG GTCCTACTCC CCCC GGGTGT
 2351 CCAATGATGT GAAGCAGCTG ACTGAGGCTG TGCAGAAGAT CACCACTGAG
 GGTACTACA CTTCGTCGAC TGA CTCCGAC ACGTCTTCTA GTGGTGACTC
 2401 TCCATGTGTA TCTGGGGCAA GACCCCAAG TTCAAGCTGC CCATCCAGAA
 AGGTAACT AGACCCGTT CTGGGGGTTT AAGTTCGACG GGTAGGTCTT
 2451 GGAGACCTGG GAGACCTGGT GGA CTGAGTA CTGGCAGGCC ACCTGGATCC
 CCTCTGGACC CTCTGGACCA CCTGACTCAT GACCGTCCGG TGGACCTAGG
 2501 CTGAGTGGGA GTTTGTGAAC ACCCCCCCCC TGGTGAAGCT GTGGTACCAG
 GACTCACCTT CAAACACTTG TGGGGGGGGG ACCACTTCGA CACCATGGTC
 2551 CTGGAGAAGG AGCCCATTTGT GGGGGCTGAG ACCTTCTATG TGGCTGGGGC
 GACCTCTTCC TCGGGTAACA CCCCCGACTC TGGGAAGATAC ACCGACCCCG
 2601 TGCCAACAGG GAGACCAAGC TGGGCAAGGC TGGCTATGTG ACCAACAGGG
 ACGGTTGTCC CTCTGGTTTG ACCCGTTCCG ACCGATACAC TGGTTGTCCC
 2651 GCAGGCAGAA GGTGGTGACC CTGACTGACA CCACCAACCA GAAGACTGCC
 CGTCCGTCTT CCACCACTGG GACTGACTGT GGTGGTTGGT CTTCTGACGG
 2701 CTCCAGGCCA TCTACCTGGC CCTCCAGGAC TCTGGCCTGG AGGTGAACAT
 GAGGTCCGGT AGATGGACCG GGAGGTCCTG AGACCGGACC TCCACTTGTA
 2751 TGTGACTGCC TCCCAGTATG CCCTGGGCAT CATCCAGGCC CAGCCTGATC
 AACTGACGG AGGGTCATAC GGGACCCGTA GTAGSTCCGG CTCGGACTAG

Figure 26C

2801 AGTCTGAGTC TCTGGTG AACCAGATCA TTGAGCAGCT GATCAAGG
 TCAGACTCAG ACTCGACCAC TTGGTCTAGT AACTCGTCGA CTAGTCTTC

2851 GAGAAGGTGT ACCTGGCCTG GGTGCCTGCC CACAAGGGCA TTGGGGGCAA
 CTCTTCCACA TGGACCGGAC CCACGGACGG GTGTTCCCGT AACCCCGGT

2901 TGAGCAGGTG GACAAGCTGG TGTCTGCTGG CATCAGGAAG GTGCTGTTC
 ACTCGTCCAC CTGTTTCGACC ACAGACGACC GTAGTCTTTC CACGACAAGG

2951 TGGATGGCAT TGACAAGGCC CAGGATGAGC ATGAGAAGTA CCACTCCAAC
 ACCTACCGTA ACTGTTCCGG GTCCTACTCG TACTCTTCAT GGTGAGGTTG

3001 TGGAGGGCTA TGGCCTCTGA CTTCAACCTG CCCCCTGTGG TGGCTAAGGA
 ACCTCCCGAT ACCGGAGACT GAAGTTGGAC GGGGGACACC ACCGATTCTT

3051 GATTGTGGCC TCCTGTGACA AGTGCCAGCT GAAGGGGGAG GCCATGCATG
 CTAACACCGG AGGACACTGT TCACGGTCGA CTTCCCCCTC CGGTACGTAC

3101 GGCAGGTGGA CTGCTCCCTT GGCATCTGGC AGCTGGCCTG CACCCACCTG
 CCGTCCACCT GACGAGGGGA CCGTAGACCG TCGACCGGAC GTGGGTGGAC

3151 GAGGGCAAGG TGATCCTGGT GGCTGTGCAT GTGGCCTCCG GCTACATTGA
 CTCCCGTTCC ACTAGGACCA CCGACACGTA CACCGGAGGC CGATGTAAT

3201 GGCTGAGGTG ATCCCTGCTG AGACAGGCCA GGAGACTGCC TACTTCCTGC
 CCGACTCCAC TAGGGACGAC TCTGTCCGGT CCTCTGACGG ATGAAGGACG

3251 TGAAGCTGGC TGGCAGGTGG CCTGTGAAGA CCATCCACAC TGCCAATGGC
 ACTTCGACCG ACCGTCCACC GGACACTTCT GGTAGGTGTG ACGGTTACCG

3301 TCCAACCTCA CTGGGGCCAC AGTGAGGGCT GCCTGCTGGT GGGCTGGCAT
 AGGTTGAAGT GACCCCGGTG TCACTCCCGA CGGACGACCA CCCGACCGTA

3351 CAAGCAGGAG TTTGGCATCC CCTACAACCC CCAGTCCCAG GGGGTGGTGG
 GTTCGTCTC AAACCGTAGG GGATGTTGGG GGTGAGGGTC CCCCACCACC

3401 CCTCCATGAA CAAGGAGCTG AAGAAGATCA TTGGGCAGGT GAGGGACCAG
 GGAGGTACTT GTTCCTCGAC TTCTTCTAGT AACCCGTCCA CTCCCTGGTC

3451 GCTGAGCACC TGAAGACAGC TGTGCAGATG GCTGTGTTC TCCACAACCT
 CGACTCGTGG ACTTCTGTCT ACACGTCTAC CGACACAAGT AGGTGTTGAA

3501 CAAGAGGAAG GGGGGCATCG GGGGCTACTC CGCTGGGGAG AGGATTGTGG
 GTTCTCCTTC CCCCCGTAGC CCCCAGTAGG GCGACCCCTC TCCTAACACC

3551 ACATCATTCG CACAGACATC CAGACCAAGG AGCTCCAGAA GCAGATCACC
 TGTAGTAACG GTGTCTGTAG GTCTGGTTCC TCGAGGTCTT CGTCTAGTGG

3601 AAGATCCAGA ACTTCAGGGT GTACTACAGG GACTCCAGGA ACCCCCTGTG
 TTCTAGGTCT TGAAGTCCCA CATGATGTCC CTGAGGTCTT TGGGGGACAC

3651 GAAGGGCCCT GCCAAGCTGC TGTGGAAGGG GGAGGGGGCT GTGGTGATCC
 CTTCCCGGGA CGGTTTCGACG ACACCTTCCC CTTCCCCGA CACCACTAGG

3701 AGGACAATCT TGACATCAAG GTGGTGCCCA GGAGGAAGGC CAAGATCATC
 TCCTGTTGAG ACTGTAGTTC CACCACGGGT CTCCTTCCG GTTCTAGTAG

Figure 26 D

3751 AGGGACTATG CAGCAGAT GGCTGGGGAT GACTGTGTGG CCTCCATCA
TCCCTGATAC CTTCTGTCTA CCGACCCCTA CTGACACACC GGAGGTCTGT

3801 GGATGAGGAC TAAAGCCCGG GCAGATCTGC TGTGCCTTCT AGTTGCCAGC
CCTACTCCTG ATTTCCGGCC CGTCTAGACG ACACGGAAGA TCAACGGTCG

3851 CATCTGTTGT TTGCCCCCTC CCCGTGCCTT CCTTGACCCT GGAAGGTGCC
GTAGACAACA AACGGGGAGG GGGCACGGAA GGAACGGGA CCTTCCACGG

3901 ACTCCCACTG TCCTTTCCTA ATAAAATGAG GAAATTGCAT CGCATTTGTCT
TGAGGGTGAC AGGAAAGGAT TATTTTACTC CTTTAACGTA GCGTAACAGA

3951 GAGTAGGTGT CATTCTATTC TGGGGGGTGG GGTGGGGCAG GACAGCAAGG
CTCATCCACA GTAAGATAAG ACCCCCCACC CCACCCCGTC CTGTCGTTCC

4001 GGGAGGATTG GGAAGACAAT AGCAGGCATG CTGGGGATGC GGTGGGCTCT
CCCTCCTAAC CCTTCTGTTA TCGTCCGTAC GACCCCTACG CCACCCGAGA

4051 ATGGCCGATC GGCGCGCCGT ACTGAAATGT GTGGGCGTGG CTTAAGGGTG
TACCGGCTAG CCGCGCGGCA TGACTTTACA CACCCGCACC GAATTTCCAC

4101 GGAAAGAATA TATAAGGTGG GGGTCTTATG TAGTTTTGTA TCTGTTTTGC
CCTTCTTAT ATATTCCACC CCCAGAATAC ATCAAAACAT AGACAAAACG

4151 AGCAGCCGCC GCCGCCATGA GCACCAACTC GTTTGATGGA AGCATTTGTGA
TCGTCGGCGG CGCGGTACT CGTGGTTGAG CAAACTACCT TCGTAACACT

4201 GCTCATATTT GACAACGCGC ATGCCCCCAT GGGCCGGGGT GCGTCAGAAT
CGAGTATAAA CTGTTGCGCG TACGGGGGTA CCCGGCCCCA CGCAGTCTTA

4251 GTGATGGGCT CCAGCATTGA TGGTCGCCCC GTCTTGCCCG CAACTCTAC
CACTACCCGA GGTGTAACCT ACCAGCGGGG CAGGACGGGC GTTTGAGATG

4301 TACCTTGACC TACGAGACCG TGTCTGGAAC GCCGTTGGAG ACTGCAGCCT
ATGGAACCTG ATGCTCTGGC ACAGACCTTG CGGCAACCTC TGACGTCGGA

4351 CCGCCGCCGC TTCAGCCGCT GCAGCCACCG CCCGCGGGAT TGTGACTGAC
GGCGGCGGCG AAGTCGGCGA CGTCGGTGGC GGGCGCCCTA ACACTGACTG

4401 TTTGCTTTCC TGAGCCCGCT TGCAAACAGT GCAGCTTCCC GTTCATCCGC
AAACGAAAGG ACTCGGGCGA ACGTTTGTC ACGTGAAGGG CAAGTAGGCG

4451 CCGCGATGAC AAGTTGACGG CTCTTTTGGC ACAATTGGAT TCTTTGACCC
GGCGCTACTG TTCAACTGCC GAGAAAACCG TGTTAACCTA AGAACTGGG

4501 GGGAACTTAA TGTGTTTCT CAGCAGCTGT TGGATCTGCG CCAGCAGGTT
CCCTTGAATT ACAGCAAAGA GTCGTCGACA ACCTAGACGC GGTGCTCCAA

4551 TCTGCCCTGA AGGCTTCCTC CCCTCCCAAT GCGGTTTAAA ACATAAATAA
AGACGGGACT TCCGAAGGAG GGGAGGGTTA CGCCAAATTT TGTATTTATT

4601 AAAACCAGAC TCTGTTTGA TTTGGATCAA GCAAGTGTCT TGCTGTCTTT
TTTTGGTCTG AGACAAACCT AAACCTAGTT CGTTCACAGA ACGACAGAAA

4651 ATTTAGGGGT TTTGCGCGCG CGGTAGGCCC GGGACCAGCG GTCTCGGTCTG
TAAATCCCCA AAACGCGCGC GCCATCCGGG CCCTGGTCTG CAGAGCCAGC

Figure 26E

4701 TTGAGGGTCC TGTGTATTTT TTCCAGGACG TGGTAAAGGT GACTCTCTAT
 AACTCCCAGG AATAAAA AAGGTCCTGC ACCATTTCCTA CTGAGA A
 4751 GTTCAGATAC ATGGGCATAA GCCCGTCTCT GGGGTGGAGG TAGCACCCT
 CAAGTCTATG TACCCGTATT CGGGCAGAGA CCCCACCTCC ATCGTGGTGA
 4801 GCAGAGCTTC ATGCTGCGGG GTGGTGTGT AGATGATCCA GTCGTAGCAG
 CGTCTCGAAG TACGACGCCC CACCACAACA TCTACTAGGT CAGCATCGTC
 4851 GAGCGCTGGG CGTGGTGCCT AAAAATGTCT TTCAGTAGCA AGCTGATTGC
 CTCGCGACCC GCACCACGGA TTTTACAGA AAGTCATCGT TCGACTAACG
 4901 CAGGGGCAGG CCCTTGGTGT AAGTGTTCAC AAAGCGGTTA AGCTGGGATG
 GTCCCCGTCC GGAACCCACA TTCACAAATG TTTGCCAAT TCGACCCCTAC
 4951 GGTGCATACG TGGGGATATG AGATGCATCT TGGACTGTAT TTTTAGGTTG
 CCACGTATGC ACCCTATAC TCTACGTAGA ACCTGACATA AAAATCCAAC
 5001 GCTATGTTCC CAGCCATATC CCTCCGGGA TTCATGTTGT GCAGAACCAC
 CGATACAAGG GTCGGTATAG GGAGGCCCT AAGTACAACA CGTCTGGTG
 5051 CAGCACAGTG TATCCGGTGC ACTTGGGAAA TTTGTCTATG AGCTTAGAAG
 GTCGTGTCAC ATAGGCCAGG TGAACCTTT AAACAGTACA TCGAATCTTC
 5101 GAAATGCGTG GAAGAACTTG GAGACGCCCT TGTGACCTCC AAGATTTTCC
 CTTTACGCAC CTTCTGAAC CTCTCGGGA AACTGGAGG TTCTAAAAGG
 5151 ATGCATTCTG CCATAATGAT GGCAATGGGC CCACGGGCGG CGGCCTGGGC
 TACGTAAAGCA GGTATTACTA CCGTTACCCG GGTGCCCGCC GCCGGACCCG
 5201 GAAGATATTT CTGGGATCAC TAACGCATA GTTGTGTTCC AGGATGAGAT
 CTTCTATAAA GACCCTAGTG ATTGCAGTAT CAACACAAGG TCCTACTCTA
 5251 CGTCATAGGC CATTTTACAA AAGCGCGGGC GGAGGGTGCC AGACTGCGGT
 GCAGTATCCG GTAAAATGT TTCGCGCCCG CCTCCACGG TCTGACGCCA
 5301 ATAATGGTTC CATCCGCCCC AGGGGCGTAG TTACCCTCAC AGATTTGCAT
 TATTACCAAG GTAGGCCGGG TCCCCGCATC AATGGGAGTG TCTAAACGTA
 5351 TTCCCACGCT TTGAGTTCAG ATGGGGGAT CATGTCTACC TCGGGGGCGA
 AAGGGTGCGA AACTCAAGTC TACCCCTTA GTACAGATGG ACGCCCGCT
 5401 TGAAGAAAAC GGTTCGCGG GTAGGGGAGA TCAGCTGGGA AGAAAGCAGG
 ACTTCTTTTG CCAAAGGCC CATCCCTCT AGTCGACCT TCTTTCGTCC
 5451 TTCCTGAGCA GCTGCGACTT ACCGCAGCCG GTGGGCCCCT AAATCACACC
 AAGGACTCGT CGACGCTGAA TGGCGTCGGC CACCCGGGCA TTTAGTGTGG
 5501 TATTACCGGC TGCAACTGGT AGTTAAGAGA GCTGCAGCTG CCGTCATCCC
 ATAATGGCCG ACGTTGACCA TCAATTCTCT CGACGTCGAC GGCAGTAGGG
 5551 TGAGCAGGGG GGGCACTTCG TTAAGCATGT CCCTGACTCG CATGTTTTCC
 ACTCGTCCCC CCGGTGAAGC AATTCGTACA GGGACTGAGC GTACAAAAGG
 5601 CTGACCAAAT CCGCCAGAAG GCGCTCGCG CCCAGCGATA GCAGTTCTTG
 GACTGGTTTA GCGGCTCTTC CCGAGCGGC GGGTCGCTAT CGTCAAGAAC

Figure 26F

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5651 CAAGGAAGCA AATTTTCA ACGGTTGAG ACCGTCCGCC GTAGGCATC
      GTTCCTTCGT TTCAAAAAGT TGCCAAACTC TGGCAGGCGG CATCCGTACG

5701 TTTTGAGCGT TTGACCAAGC AGTTCCAGGC GGTCCACAG CTCGGTCACC
      AAAACTCGCA AACTGGTTCG TCAAGGTCCG CCAGGGTGTC GAGCCAGTGG

5751 TGCTCTACGG CATCTCGATC CAGCATATCT CCTCGTTTCG CGGGTTGGGG
      ACGAGATGCC GTAGAGCTAG GTCGTATAGA GGAGCAAAGC GCCCAACCCC

5801 CGGCTTTTCG TGTACGGCAG TAGTCGGTGC TCGTCCAGAC GGGCCAGGGT
      GCCGAAAGCG ACATGCCGTC ATCAGCCACG AGCAGGTCTG CCCGGTCCCA

5851 CATGTCTTTC CACGGGCGCA GGGTCCTCGT CAGCGTAGTC TGGGTCACGG
      GTACAGAAAG GTGCCCGCGT CCCAGGAGCA GTCGCATCAG ACCCAGTGCC

5901 TGAAGGGGTG CGCTCCGGGC TGC GCGCTGG CCAGGGTCCG CTTGAGGCTG
      ACTTCCCCAC GCGAGGCCCG ACGCGCGACC GGTCCACGC GAACTCCGAC

5951 GTCTGCTGG TGCTGAAGCG CTGCGGTCT TCGCCTGCG CGTCGGCCAG
      CAGGACGACC ACGACTTCGC GACGGCCAGA AGCGGGACGC GCAGCCGGTC

6001 GTAGCATTTG ACCATGGTGT CATAGTCCAG CCCCTCCGCG GCGTGGCCCT
      CATCGTAAAC TGGTACCACA GTATCAGGTC GGGGAGGCGC CGCACCGGGA

6051 TGGCGCGCAG CTTGCCCTTG GAGGAGGCGC CGCACGAGGG GCAGTCAGA
      ACCGCGCGTC GAACGGGAAC CTCCTCCGCG GCGTGCTCCC CGTCACGTCT

6101 CTTTTGAGGG CGTAGAGCTT GGGCGCGAGA AATACCGATT CCGGGGAGTA
      GAAACTCCC GCATCTCGAA CCCGCGCTCT TTATGGCTAA GGGCCCTCAT

6151 GGCATCCGCG CCGCAGGCCC CGCAGACGGT CTCGCATTCC ACGAGCCAGG
      CCGTAGGCGC GCGTCCGGG GCGTCTGCCA GAGCGTAAGG TGCTCGGTCC

6201 TGAGCTCTGG CCGTTCGGGG TCAAAAACCA GGTTCCCCC ATGCTTTTTG
      ACTCGAGACC GGCAAGCCCC AGTTTTTGGT CCAAAGGGGG TACGAAAAAC

6251 ATGCGTTTCT TACCTCTGGT TTCCATGAGC CGGTGTCCAC GTCGGGTGAC
      TACGCAAAGA ATGGAGACCA AAGGTACTCG GCCACAGGTG CGAGCCACTG

6301 GAAAAGGCTG TCCGTGTCCC CGTATACAGA CTTGAGAGGC CTGTCTCGA
      CTTTCCGAC AGGCACAGGG GCATATGTCT GAACTCTCCG GACAGGAGCT

6351 GCGGTGTTC GCGGTCTTCC TCGTATAGAA ACTCGGACCA CTCTGAGACA
      CGCCACAAGG CGCCAGGAGG AGCATATCTT TGAGCCTGGT GAGACTCTGT

6401 AAGGCTCGCG TCCAGGCCAG CACGAAGGAG GCTAAGTGGG AGGGGTAGCG
      TTCCGAGCGC AGGTCCGGTC GTGCTTCCTC CGATTCAACC TCCCCATCGC

6451 GTCGTTGTCC ACTAGGGGGT CCACTCGCTC CAGGGTGTGA AGACACATGT
      CAGCAACAGG TGATCCCCA GGTGAGCGAG GTCCCACT TCTGTGTACA

6501 CGCCCTCTTC GGCATCAAGG AAGGTGATTG GTTTGTAGGT GTAGGCCACG
      GCGGGAGAAG CCGTAGTTCC TTCCACTAAC CAAACATCCA CATCCGGTGC

6551 TGACCGGGTG TTCCTGAAGG GGGGCTATAA AAGGGGTGG GGGCGCGTTC
      ACTGGCCCCA AAGGACTTCC CCCCATATT TTCCCCACC CCCGCGCAAG

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Figure 266

6601 GTCCTCACTC TCTTCCGCAT CGCTGTCTGC GAGGGCCAGG TGTGTGCTTG
 CAGGAGTGAG AAGGCGTA GCGACAGACG CTCCCGGTGC ACAACGAC
 6651 AGTACTCCCT CTGAAAAGCG GGCATGACTT CTGCGCTAAG ATTGTCACTT
 TCATGAGGGA GACTTTTTCG CCGTACTGAA GACGCGATTG TAACAGTCAA
 6701 TCCAAAAACG AGGAGGATTT GATATTCACT TGGCCCGCGG TGATGCCTTT
 AGGTTTTTGC TCCTCCTAAA CTATAAGTGG ACCGGGCGCC ACTACGGAAA
 6751 GAGGGTGGCC GCATCCATCT GGTGAGAAAA GACAATCTTT TTGTTGTCAA
 CTCCCACCGG CGTAGGTAGA CCAGTCTTTT CTGTTAGAAA AACAACAGTT
 6801 GCTTGGTGGC AAACGACCCG TAGAGGGCGT TGGACAGCAA CTGGCGATG
 CGAACCACCG TTTGCTGGGC ATCTCCCGCA ACCTGTCTGT GAACCGCTAC
 6851 GAGCGCAGGG TTTGGTTTTT GTCGCGATCG GCGCGCTCCT TGGCCGCGAT
 CTCGCGTCCC AAACCAAAAA CAGCGCTAGC GCGCGAGGA ACCGGCGCTA
 6901 GTTTAGCTGC ACGTATTTCG GCGCAACGCA CCGCCATTTC GGAAAGACGG
 CAAATCGACG TGCATAAGCG CGCGTTGCGT GCGCGTAAGC CCTTTCTGCC
 6951 TGGTGCCTGC GTCGGGCACC AGGTGCACGC GCCAACCGCG GTTGTGCAGG
 ACCACGCGAG CAGCCCGTGG TCCACGTGCG CGGTTGGCGC CAACACGTCC
 7001 GTGACAAGGT CAACGCTGGT GGCTACCTCT CCGCGTAGGC GCTCGTTGGT
 CACTGTTCCA GTTGCACCA CCGATGGAGA GCGCGATCCG CGAGCAACCA
 7051 CCAGCAGAGG CGGCCGCCCT TGCAGGAGCA GAATGGCGGT AGGGGGTCTA
 GGTCTCTCC GCGGCGGGA ACGCGCTCGT CTTACCGCCA TCCCCAGAT
 7101 GCTGCGTCTC GTCCGGGGGG TCTGCGTCCA CGGTAAAGAC CCCGGGCAGC
 CGACGCAGAG CAGGCCCCC AGACGCAGGT GCCATTTCTG GGGCCCGTGC
 7151 AGGCGCGCGT CGAAGTAGTC TATCTTGCAT CTTGCAAGT CTAGCGCCTG
 TCCGCGCGCA GCTTCATCAG ATAGAACGTA GGAACGTTCA GATCGCGGAC
 7201 CTGCCATGCG CGGGCGGCAA GCGCGCGCTC GTATGGGTTG AGTGGGGGAC
 GACGGTACGC GCCCGCCGTT CCGCGCGAG CATACCCAAC TCACCCCTG
 7251 CCCATGGCAT GGGGTGGGTG AGCGCGGAGG CGTACATGCC GCAAAATGTCG
 GGGTACCGTA CCCACCCAC TCGCGCCTCC GCATGTACGG CGTTTACAGC
 7301 TAAACGTAGA GGGGCTCTCT GAGTATTCCA AGATATGTAG GGTAGCATCT
 ATTTGCATCT CCCCAGAGA CTCATAAGGT TCTATACATC CCATCGTAGA
 7351 TCCACCGCGG ATGCTGGCGC GCACGTAATC GTATAGTTTC TGCGAGGGAG
 AGGTGGCGCC TACGACCGCG CGTGCATTAG CATATCAAGC ACGCTCCCTC
 7401 CGAGGAGGTC GGGACCGAGG TTGCTACGGG CGGGCTGCTC TGCTCGGAAG
 GCTCCTCCAG CCCTGGCTCC AACGATGCCC GCGGACGAG ACGAGCCTTC
 7451 ACTATCTGCC TGAAGATGGC ATGTGAGTTG GATGATATGG TTGGACGCTG
 TGATAGACGG ACTTCTACCG TACACTCAAC CTACTATACC AACCTGCGAC
 7501 GAAGACGTTG AAGCTGGCGT CTGTGAGACC TACCGCGTCA CGCACGAAGG
 CTTCTGCAAC TTCGACCGCA GACACTCTGG ATGGCGCAGT GCGTGCTTCC

Figure 26 H

7551 AGGCGTAGGA GCGCAGC TTGTTGACCA GCTCGGCGGT GACCTGCG
 TCCGCATCCT CAGCGCGTCG AACAACTGGT CGAGCCGCCA CTGGACGTGC
 7601 TCTAGGGCGC AGTAGTCCAG GGTTCCTTG ATGATGTCAT ACTTATCCTG
 AGATCCCGCG TCATCAGGTC CCAAAGGAAC TACTACAGTA TGAATAGGAC
 7651 TCCCTTTTTT TTCCACAGCT CGCGGTTGAG GACAACTCT TCGCGGTCTT
 AGGGAAAAAA AAGGTGTCGA GCGCCAACTC CTGTTTGAGA AGCGCCAGAA
 7701 TCCAGTACTC TTGGATCGGA AACCCGTCGG CCTCCGAACG GTAAGAGCCT
 AGGTCATGAG AACCTAGCCT TTGGGCAGCC GGAGGCTTGC CATTCTCGGA
 7751 AGCATGTAGA ACTGGTTGAC GGCCTGGTAG GCGCAGCATC CCTTTTCTAC
 TCGTACATCT TGACCAACTG CCGGACCATC CGCGTCGTAG GGAAAGATG
 7801 GGGTAGCGCG TATGCCTGCG CGGCCTTCCG GAGCGAGGTG TGGGTGAGCG
 CCCATCGCGC ATACGGACGC GCCGGAAGGC CTCGCTCCAC ACCCACTCGC
 7851 CAAAGGTGTC CCTGACCATG ACTTTGAGGT ACTGGTATTT GAAGTCAGTG
 GTTTCCACAG GGACTGGTAC TGAAACTCCA TGACCATAAA CTTCAAGTCAC
 7901 TCGTCGCATC CGCCCTGCTC CCAGAGCAAA AAGTCCGTGC GCTTTTGGGA
 AGCAGCGTAG GCGGGACGAG GGTCCTGTTT TTCAGGCACG CGAAAAACCT
 7951 ACGCGGATTT GGCAGGGCGA AGGTGACATC GTTGAAGAGT ATCTTCCCG
 TGCGCCATAA CCGTCCCGCT TCCACTGTAG CAACTTCTCA TAGAAAGGGC
 8001 CGCGAGGCAT AAAGTTGCGT GTGATGCGGA AGGGTCCCGG CACCTCGGAA
 GCGCTCCGTA TTTCAACGCA CACTACGCCT TCCCAGGGCC GTGGAGCCTT
 8051 CGGTGTGTAA TTACCTGGGC GCGGAGCACG ATCTCGTCAA AGCCGTTGAT
 GCCAACAAAT AATGGACCCG CCGCTCGTGC TAGAGCAGTT TCGGCAACTA
 8101 GTTGTGGCCC ACAATGTAAA GTTCCAAGAA GCGCGGGATG CCCTTGATGG
 CAACACCGGG TGTTACATTT CAAGTTCTT CGCGCCCTAC GGGAACTACC
 8151 AAGGCAATTT TTTAAGTTCC TCGTAGGTGA GCTCTTCAGG GGAGCTGAGC
 TTCCGTTAAA AAATCAAGG AGCATCCACT CGAGAAGTCC CCTCGACTCG
 8201 CCGTGCTCTG AAAGGGCCCA GTCTGCAAGA TGAGGGTTGG AAGCGACGAA
 GGCACGAGAC TTTCCCGGGT CAGACGTTCT ACTCCCAACC TTCGCTGCTT
 8251 TGAGCTCCAC AGGTCACGGG CCATTAGCAT TTGCAGGTGG TCGCGAAAGG
 ACTCGAGGTG TCCAGTGCCC GGTAAATCGTA AACGTCCACC AGCGCTTTCC
 8301 TCCTAAACTG GCGACCTATG GCCATTTTTT CTGGGGTGAT GCAGTAGAAG
 AGGATTTGAC CGCTGGATAC CGGTAAAAAA GACCCCACTA CGTCATCTTC
 8351 GTAAGCGGGT CTTGTTCCCA GCGGTCCCAT CCAAGGTTCC GGGCTAGGTC
 CATTGCCCCA GAACAAGGGT CGCCAGGGTA GGTTCCAAGC GCCGATCCAG
 8401 TCGCGCGGCA GTCAC TAGAG GTCATCTCC GCCGAAC TTC ATGACCAGCA
 AGCGCGCCGT CAGTGATCTC CGAGTAGAGG CGGCTTGAAG TACTGGTCGT
 8451 TGAAGGGCAC GAGCTGCTTC CCAAAGGCCC CCATCCAAGT ATAGGTCTCT
 ACTTCCCGTG CTCGACGAAG GGTTCGCGG GGTAGGTTCA TATCCAGAGA

Figure 26I

8501 ACATCGTAGG TAAAGAG ACGCTCGGTG CGAGGATGCG AGCCGA G
TGTAGCATCC ACTGTTTCTC TCGAGGCCAC GTCCTACGC TCGGCTAGCC

8551 GAAGAACTGG ATCTCCCGCC ACCAATTGGA GGAGTGGCTA TTGATGTGGT
CTTCTTGACC TAGAGGGCGG TGGTTAACCT CCTCACCAGT AACTACACCA

8601 GAAAGTAGAA GTCCCTGCGA CGGGCCGAAC ACTCGTGCTG GCTTTTGTA
CTTTCATCTT CAGGGACGCT GCGCGCTTG TGAGCACGAC CGAAAACATT

8651 AAACGTGCGC AGTACTGGCA GCGGTGCACG GGCTGTACAT CCTGCACGAG
TTTGACGCG TCATGACCGT CGCCACGTGC CCGACATGTA GGACGTGCTC

8701 GTTGACCTGA CGACCGCGCA CAAGGAAGCA GAGTGGGAAT TTGAGCCCT
CAACTGGACT GCTGGCGCGT GTTCTTCTGT CTCACCTTA AACTCGGGGA

8751 CGCCTGGCGG GTTTGGCTGG TGGTCTTCTA CTTGCGCTGC TTGTCCTGA
GCGGACCGCC CAAACCGACC ACCAGAAGAT GAAGCCGACG AACAGGAACT

8801 CCGTCTGGCT GCTCGAGGGG AGTTACGGTG GATCGGACCA CCACGCCGCG
GGCAGACCGA CGAGCTCCCC TCAATGCCAC CTAGCCTGGT GGTGCGGCGC

8851 CGAGCCCAAA GTCCAGATGT CCGCGCGCGG CGGTGCGAGC TTGATGACAA
GCTCGGGTTT CAGGTCTACA GCGCGCGGCC GCCAGCCTCG AACTACTGTT

8901 CATCGCGCAG ATGGGAGCTG TCCATGGTCT GGAGCTCCCG CGGCGTCAGG
GTAGCGCGTC TACCCTCGAC AGGTACCAGA CCTCGAGGGC GCCGCAGTCC

8951 TCAGGCGGGA GCTCCTGCAG GTTTACCTCG CATAGACGGG TCAGGGCGCG
AGTCCGCCCT CGAGGACGTC CAAATGGAGC GTATCTGCC AGTCCCGCGC

9001 GGCTAGATCC AGGTGATACC TAATTTCCAG GGGCTGGTTG GTGGCGGCGT
CCGATCTAGG TCCACTATGG ATTAAAGGTC CCCGACCAAC CACCGCCGCA

9051 CGATGGCTTG CAAGAGGCCG CATCCCCGCG GCGCGACTAC GGTACCGCGC
GCTACCGAAC GTTCTCCGGC GTAGGGGCGC CCGCTGATG CCATGGCGCG

9101 GCGGGGCGGT GGGCCGCGGG GGTGTCCTTG GATGATGCAT CTAAAAGCGG
CCGCCCCCA CCCGGCGCCC CCACAGGAAC CTACTACGTA GATTTTCGCC

9151 TGACGCGGGC GAGCCCCCGG AGGTAGGGGG GGCTCCGAC CCGCCGGGAG
ACTGCGCCCG CTCGGGGGCC TCCATCCCCC CGAGGCCTG GCGGGCCCTC

9201 AGGGGGCAGG GGCACGTCGG CGCGCGCGCG GGCAGGAGC TGGTGCTGCG
TCCCCCGTCC CCGTGCAGCC GCGGCGCGCG CCCGTCCTCG ACCACGACGC

9251 CGCGTAGGTT GCTGGCGAAC GCGACGACGC GCGGTTGAT CTCCTGAATC
GCGCATCCAA CGACCGCTTG CGCTGCTGCG CCGCCAATA GAGGACTTAG

9301 TGGCGCTCT GCGTGAAGAC GACGGGCCCG GTGAGCTTGA ACCTGAAAGA
ACCGCGGAGA CGCACTTCTG CTGCCCCGGC CACTCGAACT TGGACTTTCT

9351 GAGTTCGACA GAATCAATTT CCGTGTGCTT GACGGCGGCC TGGCGCAAAA
CTCAAGCTGT CTTAGTTAAA GCCACAGCAA CTGCCCGCG ACCGCGTTTT

9401 TCTCCTGCAC GTCTCCTGAG TTGTCTTGAT AGGCGATCTC GGCCATGAAC
AGAGGACGTG CAGAGGACTC AACAGAACTA TCCGCTAGAG CCGGTACTTG

Figure 26 J

9451 TGCTCGATCT C CTCTG GAGATCTCCG CGTCCGGCTC GCTCCA T
 ACGAGCTAGA GAAGGAGGAC CTCTAGAGGC GCAGGCCGAG CGAGGTGCCA
 9501 GGCGGCGAGG TCGTTGGAAA TCGGGGCCAT GAGCTGCGAG AAGGCGTTGA
 CCGCCGCTCC AGCAACCTTT ACGCCCGGTA CTCGACGCTC TTCCGCAACT
 9551 GGCTTCCCTC GTTCCAGACG CGGCTGTAGA CCACGCCCCC TTCGGCATCG
 CCGGAGGGAG CAAGGTCTGC GCCGACATCT GGTGCGGGG AAGCCGTAGC
 9601 CGGGCGCGCA TGACCACCTG CGCGAGATTG AGCTCCACGT GCCGGGCGAA
 GCCCGCGCGT ACTGGTGGAC GCGCTCTAAC TCGAGGTGCA CGGCCCGCTT
 9651 GACGGCGTAG TTTCGAGGC GCTGAAAGAG GTAGTTGAGG GTGGTGGCGG
 CTGCCGCATC AAAGCGTCCG CGACTTTCTC CATCAACTCC CACCACCGCC
 9701 TGTGTTCTGC CACGAAGAAG TACATAACCC AGCGTCGCAA CGTGATTTCG
 ACACAAGACG GTGCTTCTTC ATGTATTGGG TCGCAGCGTT GCACCTAAGC
 9751 TTGATATCCC CCAAGGCCTC AAGGCGCTCC ATGGCCTCGT AGAAGTCCAC
 AACTATAGGG GTTCCGGAG TTCCGCGAGG TACCGGAGCA TCTTCAGGTG
 9801 GGCGAAGTTG AAAAAGTGGG AGTTGCGCGC CGACACGGTT AACTCCTCCT
 CCGCTTCAAC TTTTGTACCC TCAACGCGCG GCTGTGCCAA TTGAGGAGGA
 9851 CCAGAAGACG GATGAGCTCG GCGACAGTGT CGCGCACCTC GCGCTCAAAG
 GGTCTTCTGC CTACTCGAGC CGCTGTCACA GCGCGTGGAG CGCGAGTTTC
 9901 GCTACAGGGG CCTCTTCTTC TTCTTCAATC TCCTCTTCCA TAAGGGCCTC
 CGATGTCCCC GGAGAAGAAG AAGAAGTTAG AGGAGAAGGT ATTCCCGGAG
 9951 CCCTTCTTCT TCTTCTGGCG GCGGTGGGGG AGGGGGGACA CGGCGGCGAC
 GGAAGAAGA AGAAGACCGC CGCCACCCCC TCCCCCTGT GCCGCCGCTG
 10001 GACGGCGCAC CGGGAGGCGG TCGACAAAGC GTCGATCAT CTCCCCGCGG
 CTGCCGCGTG GCCCTCCGCC AGCTGTTTCG CGAGCTAGTA GAGGGGCGCC
 10051 CGACGGCGCA TGGTCTCGGT GACGGCGCGG CCGTTCTCGC GGGGGCGCAG
 GCTGCCGCGT ACCAGAGCCA CTGCCGCGCC GGCAAGAGCG CCCCCGCGTC
 10101 TTGGAAGACG CCGCCCGTCA TGTCCCGGTT ATGGGTTGGC GGGGGGCTGC
 AACCTTCTGC GCGGGGCACT ACAGGGCCAA TACCCAACCG CCCCCGACG
 10151 CATGCGGCAG GGATACGGCG CTAACGATGC ATCTCAACAA TTGTTGTGTA
 GTACGCCGTC CCTATGCCGC GATTGCTACG TAGAGTTGTT AACAAACAT
 10201 GGTACTCCGC CGCCGAGGGA CCTGAGCGAG TCCGCATCGA CCGGATCGGA
 CCATGAGGCG GCGGCTCCCT GGACTCGCTC AGGCGTAGCT GGCCTAGCCT
 10251 AAACCTCTCG AGAAAGGCGT CTAACGATC ACAGTCGCAA GGTAGGCTGA
 TTTGGAGAGC TCTTCCGCA GATTGCTCAG TGTCAGCGTT CCATCCGACT
 10301 GCACCGTGGC GGGCGGCGC GGGCGGCGT CGGGGTTGTT TCTGGCGGAG
 CGTGGCACCG CCCGCCGTCG CCCGCCGCA GCCCAACAA AGACCGCCTC
 10351 GTGCTGCTGA TGATGTAATT AAAGTAGGCG GTCTTGAGAC GCGGATGGT
 CACGACGACT ACTACATTAA TTTCATCCGC CAGAACTCTG CCGCCTACCA

Figure 26 K

10401 CGACAGAAGC AATGTGTCCT TGGGTCCGGC CTGCTGAATG CGCAGGCTT
 GCTGCTCTTCG TGTACAGGA ACCCAGGCCG GACGACTTAC GCGTCCCTCA
 10451 CGGCCATGCC CCAGGCTTCG TTTTGACATC GGCAGGCTC TTTGTAGTAG
 GCCGGTACGG GGTCCGAAGC AAAACTGTAG CCGCGTCCAG AAACATCATC
 10501 TCTTGCATGA GCCTTTCTAC CGGCACCTCT TCTTCTCCTT CCTCTTGCTC
 AGAACGTACT CGGAAAGATG GCCGTGAAGA AGAAGAGGAA GGAGAACAGG
 10551 TGCATCTCTT GCATCTATCG CTGCGGCGGC GCGGAGTTT GGCCGTAGGT
 ACGTAGAGAA CAGTAGATAG GACGCCGCCG CCGCCTCAA CCGGCATCCA
 10601 GCGCCCTCTT TCCTCCCATG CGTGTGACCC CGAAGCCCTT CATCGGCTGA
 CCGCGGAGAG AGGAGGGTAC GCACACTGGG GCTTCGGGGA GTAGCCGACT
 10651 AGCAGGGCTA GGTGCGGAC AACCGCTCG GCTAATATGG CCTGCTGCAC
 TCGTCCCGAT CCAGCCGCTG TTGCGCGAGC CGATTATACC GGACGACGTG
 10701 CTGCGTGAGG GTAGACTGGA AGTCATCCAT GTCCACAAAG CCGTGGTATG
 GACGCACTCC CATCTGACCT TCAGTAGGTA CAGGTGTTTC GCCACCATAC
 10751 CGCCCGTGTG GATGGTGTAA GTGCAGTTGG CCATAACGGA CCAGTTAAGC
 GCGGGCACAA CTACCACATT CACGTCAACC GGTATTGCCT GGTCAATTGC
 10801 GTCTGGTGAC CCGGCTGCGA GAGCTCGGTG TACCTGAGAC GCGAGTAAGC
 CAGACCACTG GCGCGACGCT CTCGAGCCAC ATGGACTCTG CGCTCATTCG
 10851 CCTCGAGTCA AATACGTAGT CGTTGCAAGT CCGCACCAGG TACTGGTATC
 GGAGCTCAGT TTATGCATCA GCAACGTTCA GCGGTGGTCC ATGACCATAG
 10901 CCACCAAAAA GTGCGGCGGC GGCTGGCGGT AGAGGGGCCA GCGTAGGGTG
 GGTGTTT TTTT CACGCCGCCG CCGACCGCCA TCTCCCCGGT CGCATCCCA
 10951 GCGGGGGCTC CCGGGGCGAG ATCTTCCAAC ATAAGGCGAT GATATCCGTA
 CGGCCCCGAG GCCCCGCTC TAGAAGGTTG TATTCCGCTA CTATAGGCAT
 11001 GATGTACCTG GACATCCAGG TGATGCCGGC GCGGTGGTG GAGGCGCGCG
 CTACATGGAC CTGTAGGTCC ACTACGGCCG CCGCCACCAC CTCCGCGCGC
 11051 GAAAGTCGCG GACGCGGTTT CAGATGTTGC GCAGCGGCAA AAAGTGCTCC
 CTTCAGCGC CTGCGCCAAG GTCTACAACG CGTCGCCGTT TTTCACGAGG
 11101 ATGGTCGGGA CGCTCTGGCC GGTCAGGCGC GCGCAATCGT TGACGCTCTA
 TACCAGCCCT GCGAGACCGG CCAGTCCGCG CCGGTTAGCA ACTGCGAGAT
 11151 GACCGTGCAA AAGGAGAGCC TGTAAGCGGG CACTCTTCCG TGGTCTGGTG
 CTGGCACGTT TTCCTCTCGG ACATTGCCCC GTGAGAAGGC ACCAGACCAC
 11201 GATAAATTCG CAAGGGTATC ATGGCGGACG ACCGGGGTTC GAGCCCCGTA
 CTATTTAAGC GTTCCCATAG TACCGCTGCG TGGCCCCAAG CTCGGGGCAT
 11251 TCCGGCCGTC CCGCGTGATC CATGCGGTTA CCGCCCGCGT GTCGAACCCA
 AGGCCGGCAG GCGGCACTAG GTACGCCAAT GCGGGGCGCA CAGCTTGGGT
 11301 GGTGTGCGAC GTCAGACAAC GGGGGAGTGC TCCTTTTGGC TTCCTTCCAG
 CCACACGCTG CAGTCTGTTG CCCCTCAGC AGGAAAACCG AAGGAAGGTC

Figure 26L

11351 GCGCGGCGGC TCGCGCTA GCTTTTTTGG CCACTGGCCG CGCGCACT
CGCGCCGCCG ACACGCGGAT CGAAAAACC GGTGACCGGC GCGCGTCCCA

11401 AAGCGGTTAG GCTGGAAAGC GAAAGCATT AAGTGGCTCGC TCCCTGTAGC
TTCGCCAATC CGACCTTTCG CTTTCGTAAT TCACCGAGCG AGGGACATCG

11451 CGGAGGGTTA TTTTCCAAGG GTTGAGTCGC GGGACCCCGG GTTCGAGTCT
GCCTCCCAAT AAAAGGTTCC CAACTCAGCG CCTTGGGGGC CAAGCTCAGA

11501 CGGACCGGCC GGAATGCGGC GAACGGGGGT TTGCCTCCCC GTCATGCAAG
GCCTGGCCGG CCTGACGCCG CTTGCCCCCA AACGGAGGGG CAGTACGTTT

11551 ACCCGGCTTG CAAATTCCTC CGGAAACAGG GACGAGCCCC TTTTGTGCTT
TGGGGCGAAC GTTTAAGGAG GCCTTTGTCC CTGCTCGGGG AAAAACGAA

11601 TTCCAGATG CATCCGGTGC TCGGCGAGAT GCGCCCCCCT CCTCAGCAGC
AAGGCTCTAC GTAGGCCACG ACGCCGTCTA CGCGGGGGGA GGAGTCGTGC

11651 GGCAAGAGCA AGAGCAGCGG CAGACATGCA GGGCACCCCT CCCTCCTCCT
CCGTCTCTGT TCTCGTCGCC GTCTGTACGT CCCGTGGGAG GGGAGGAGGA

11701 ACCGCGTCAG GAGGGGCGAC ATCCGCGGTT GACGCGGCAG CAGATGGTGA
TGGCGCAGTC CTCCCCGCTG TAGGCGCCAA CTGCGCCGTC GTCTACCACT

11751 TTACGAACCC CCGCGGCGCC GGGCCCGGCA CTACCTGGAC TTGGAGGAGG
AATGCTTGGG GCGCGCGCGG CCCGGGCCGT GATGGACCTG AACCTCCTCC

11801 GCGAGGGCCT GCGCGGCTA GGAGCGCCCT CTCCTGAGCG GCACCCAAGG
CGCTCCCGGA CCGCGCCGAT CCTCGCGGGA GAGGACTCGC CGTGGGTTC

11851 GTGCAGCTGA AGCGTGATAC GCGTGAGGCG TACGTGCCGC GGCAGAACCT
CACGTGCACT TCGCACTATG CGCACTCCGC ATGCACGGCG CCGTCTTGGA

11901 GTTTCGCGAC CGCGAGGGAG AGGAGCCCGA GGAGATGCGG GATCGAAAGT
CAAAGCGCTG GCGCTCCCTC TCCTCGGGCT CCTCTACGCC CTAGCTTTCA

11951 TCCACGCAGG GCGCGAGCTG CGGCATGGCC TGAATCGCGA GCGGTTGCTG
AGGTGCGTCC CGCGCTCGAC GCCGTACCGG ACTTAGCGCT CGCCAACGAC

12001 CGCGAGGAGG ACTTTGAGCC CGACGCGCGA ACCGGGATTA GTCCCGCGCG
GCGCTCCTCC TGAAACTCGG GCTGCGCGCT TGGCCCTAAT CAGGGCGCGC

12051 CGCACACGTG GCGGCCGCGG ACCTGGTAAC CGCATACGAG CAGACGGTGA
GCGTGTGCAC CGCCGGCGGC TGGACCATTG GCGTATGCTC GTCTGCCACT

12101 ACCAGGAGAT TAACTTTCAA AAAAGCTTTA ACAACCACGT GCGTACGCTT
TGGTCTCTA ATTGAAAGTT TTTTCGAAAT TGTGTTGCA CGCATGCGAA

12151 GTGGCGCGCG AGGAGGTGGC TATAGGACTG ATGCATCTGT GGGACTTTGT
CACCGCGCGC TCCTCCACCG ATATCCTGAC TACGTAGACA CCCTGAAACA

12201 AAGCGCGCTG GAGCAAAACC CAAATAGCAA GCCGCTCATG GCGCAGCTGT
TTCGCGCGAC CTCGTTTGGG GTTTATCGTT CGCGAGTAC CGCGTCGACA

12251 TCCTTATAGT GCAGCACAGC AGGGACAACG AGGCATTCAG GGATGCGCTG
AGGAATATCA CGTCGTGTCG TCCTGTGTGC TCCGTAAGTC CCTACGCGAC

Figure 26 M

12301 CTAAACATAG T G C C C C G A G G G C C G C T G G C T G C T C G A T T T G A T A A T
G A T T T G T A T C A T C T C G G G C T C C C G G C G A C C G A C G A G C T A A A C T A T T T G T A

12351 C C T G C A G A G C A T A G T G G T G C A G G A G C G C A G C T T G A G C C T G C T G A C A A G G
G G A C G T C T C G T A T C A C C A C G T C C T C G C G T C G A A C T C G G A C C G A C T G T T C C

12401 T G G C C G C C A T C A A C T A T T C C A T G C T T A G C C T G G G C A A G T T T T A C G C C C G C
A C C G C G C G T A G T T G A T A A G G T A C G A A T C G G A C C C G T T C A A A A T G C G G G C G

12451 A A G A T A T A C C A T A C C C C T T A C G T T C C C A T A G A C A A G G A G G T A A A G A T C G A
T T C T A T A T G G T A T G G G G A A T G C A A G G G T A T C T G T T C C T C C A T T T C T A G C T

12501 G G G G T T C T A C A T G C G C A T G G C G C T G A A G G T G C T T A C C T T G A G C G A C A C C
C C C C A A G A T G T A C G C G T A C C G C G A C T T C C A C G A A T G G A A C T C G C T G C T G G

12551 T G G G C G T T T A T C G C A A C G A G C G C A T C C A C A A G C C G T G A G C G T G A G C C G G
A C C C G C A A A T A G C G T T G C T C G C G T A G G T G T T C C G G C A C T C G C A C T C G G C C

12601 C G G C G C G A G C T C A G C G A C C G C G A G C T G A T G C A C A G C C T G C A A A G G G C C C T
G C C G C G C T C G A G T C G C T G G C G C T C G A C T A C G T G T C G G A C G T T T C C G G G A

12651 G G C T G G C A C G G G C A G C G C G C A T A G A G A G G C C G A G T C C T A C T T T G A C G C G G
C C G A C C G T G C C C G T C G C C G C T A T C T C T C C G G C T C A G G A T G A A A C T G C G C C

12701 G C G C T G A C C T G C G C T G G G C C C C A A G C C G A C G C G C C C T G G A G G C A G C T G G G
C G C G A C T G G A C G C G A C C C G G G G T T C G G C T G C G C G G A C C T C C G T C G A C C C

12751 G C C G G A C C T G G C T G G C G G T G G C A C C C G C G C G C G T G G C A A C G T C G G C G G
C G G C C T G G A C C C G A C C C A C C G T G G G C G C G C G A C C G T G C A G C C G C C

12801 C G T G G A G G A A T A T G A C G A G G A C G A T G A G T A C G A G C C A G A G A C G G C G A G T
G C A C C T C C T T A T A C T G C T C C T G C T A C T C A T G C T C G G T C T C T G C C C G C T C A

12851 A C T A A G C G G T G A T G T T T C T G A T C A G A T G A T G C A A G A C G C A A C G G A C C C G G
T G A T T C G C C A C T A C A A A G A C T A G T C T A C T A C G T T C T G C G T T G C C T G G G C C

12901 C G G T G C G G G C G G C G C T G C A G A C C A G C C G T C C G G C C T T A A C T C C A C G G A C
G C C A C G C C C G C C G C G A C G T C T C G G T C G G C A G C C G G A A T T G A G T G C C T G

12951 G A C T G G C G C C A G G T C A T G G A C C G A T C A T G T C G C T G A C T G C G C G A A T C C
C T G A C C G C G G T C C A G T A C C T G G C G T A G T A C A G C G A C T G A C G C G C G T A G G

13001 T G A C G C G T T C C G G C A G C A G C G C A G G C C A A C C G G C T C T C C G C A A T T C T G G
A C T G C G C A A G G C C G T C G T C G C G T T G C C G A G A G G C G T T A A G A C C

13051 A A G C G G T G G T C C C G G C G C G C G C A A C C C C A C G C A C G A G A A G G T G C T G G C G
T T C G C C A C C A G G C C G C G C G T T T G G G G T G C G T G C T C T T C C A C G A C C G C

13101 A T C G T A A A C G C G C T G G C C G A A A C A G G G C C A T C C G G C C C G A C G A G G C C G G
T A G C A T T T G C G C G A C C G C T T T G T C C C G G T A G G C C G G G C T G C T C C G G C C

13151 C C T G G T C T A C G A C G C G C T G C T T C A G C G C G T G G C T C G T T A C A A C A G C G G C A
G G A C C A G A T G C T G C G C G A C G A A G T C G C G C A C C G A G C A A T G T T G T C G C C G T

13201 A C G T G C A G A C C A A C C T G G A C C G G C T G G T G G G G A T G T G C G C A G A G C C C G T G
T G C A C G T C T G G T T G G A C C T G C C G A C C A C C T A C A C G C G C T C C G G C A C

Figure 26 N

13251 GCGCAGCGTG A GCGCGCA GCAGCAGGGC AACCTGGGCT CCATGGTTC
CGCGTCGCAC TCGCGCGCGT CGTCGTCCCG TTGGACCCGA GGTACCAACG

13301 ACTAAACGCC TTCCTGAGTA CACAGCCCGC CAACGTGCCG CGGGGACAGG
TGATTTGCGG AAGGACTCAT GTGTCGGGCG GTTGACAGGC GCCCCTGTCC

13351 AGGACTACAC CAACTTTGTG AGCGCACTGC GGCTAATGGT GACTGAGACA
TCCTGATGTG GTTGAAACAC TCGCGTGACG CCGATTACCA CTGACTCTGT

13401 CCGCAAAGTG AGGTGTACCA GTCTGGGCCA GACTATTTTT TCCAGACCAG
GGCGTTTCAC TCCACATGGT CAGACCCGGT CTGATAAAAA AGGTCTGGTC

13451 TAGACAAGGC CTGCAGACCG TAAACCTGAG CCAGGCTTTC AAAAAGTTGC
ATCTGTTCCG GACGTCTGGC ATTTGGACTC GGTCCGAAAG TTTTGAACG

13501 AGGGGCTGTG GGGGGTGGG GCTCCACAG GCGACCGCG GACCGTGTCT
TCCCCGACAC CCCCCACGCC CGAGGGTGTG CGCTGGCGCG CTGGCACAGA

13551 AGCTTGCTGA CGCCCAACTC GCGCTGTGTG CTGCTGCTAA TAGCGCCCTT
TCGAACGACT GCGGGTTGAG CGCGGACAAC GACGACGATT ATCGCGGGAA

13601 CACGGACAGT GGCAGCGTGT CCCGGGACAC ATACCTAGGT CACTTGCTGA
GTGCCGTGTCA CCGTCGCACA GGGCCCTGTG TATGGATCCA GTGAACGACT

13651 CACTGTACCG CGAGGCCATA GGTCAGGCGC ATGTGGACGA GCATACTTTC
GTGACATGGC GCTCCGGTAT CCAGTCCGCG TACACCTGCT CGTATGAAAG

13701 CAGGAGATTA CAAGTGTGAG CCGCGCGCTG GGGCAGGAGG ACACGGGCAG
GTCTCTAAT GTTACAGTC GCGCGCGGAC CCCGTCTCC TGTGCCCCGT

13751 CCTGGAGGCA ACCCTAAACT ACCTGCTGAC CAACCGGCGG CAGAAGATCC
GGACCTCCGT TGGGATTGA TGGACGACTG GTTGGCCGCC GTCTTCTAGG

13801 CCTCGTTGCA CAGTTTAAAC AGCGAGGAGG AGCGCATTTT GCGCTACGTG
GGAGCAACGT GTCAAAATTG TCGCTCTCC TCGCGTAAAA CGCGATGCAC

13851 CAGCAGAGCG TGAGCCTTAA CCTGATGCGC GACGGGTAA CGCCCAGCGT
GTCGTCTCGC ACTCGGAATT GGAATACGCG CTGCCCCATT GCGGGTCGCA

13901 GCGCTGGAC ATGACCGCGC GCAACATGGA ACCGGGCATG TATGCCTCAA
CCGCGACCTG TACTGGCGCG CGTTGTACCT TGGCCCGTAC ATACGGAGTT

13951 ACCGGCCGTT TATCAACCGC CTAATGGACT ACTTGCAATG CGCGGCCGCC
TGGCCGGCAA ATAGTTGGCG GATTACCTGA TGAACGTAGC GCGCCGCGCG

14001 GTGAACCCCG AGTATTTAC CAATGCCATC TTGAACCCGC ACTGGCTACC
CACTTGGGGC TCATAAAGTG GTTACGGTAG AACTTGGGCG TGACCGATGG

14051 GCCCCCTGGT TTCTACACCG GGGGATTGGA GGTGCCCCGAG GGTAAACGATG
CGGGGGACCA AAGATGTGGC CCCCTAAGCT CCACGGGCTC CCATTGCTAC

14101 GATTCTCTG GGACGACATA GACGACAGCG TGTTTTCCCC GCAACCGCAG
CTAAGGAGAC CTGCTGTAT CTGCTGTGCG AAAAAAGGGG CGTTGGCGTC

14151 ACCCTGCTAG AGTTGCAACA GCGCGAGCAG GCAGAGGCGG CGCTGCGAAA
TGGGACGATC TCAACGTTGT CGCGCTCGTC CGTCTCCGCC GCGACGCTTT

Figure 260

14201 GGAAAGCTTC CCGAGGCCAA GCAGCTTGTC CGATCTAGTC GCTGCGGCTC
 CCTTTCGAAG GCTCCGGTT CGTCGAACAG GCTAGATCCG CGACGCTG
 14251 CGCGGTGAGA TGCTAGTAGC CCATTTCCAA GCTTGATAGG GTCTCTTACC
 GCGCCAGTCT ACGATCATCG GGTAAAGGTT CGAACTATCC CAGAGAATGG
 14301 AGCACTCGCA CCACCCGCCC GCGCCTGCTG GCGGAGGAGG AGTACCTAAA
 TCGTGAGCGT GGTGGGCGGG CCGGACGAC CCGCTCCTCC TCATGGATTT
 14351 CAACTCGCTG CTGCAGCCGC AGCGCGAAAA AAACCTGCCT CCGGCATTTC
 GTTGACGAC GACGTCGGCG TCGCGCTTTT TTTGGACGGA GGCCGTAAAG
 14401 CCAACAACGG GATAGAGAGC CTAGTGGACA AGATGAGTAG ATGGAAGACG
 GGTGTTGCC CTATCTCTCG GATCACCTGT TCTACTCATC TACCTTCTGC
 14451 TACGCGCAGG AGCACAGGGA CGTGCCAGGC CCGCGCCCGC CCACCCGTCC
 ATGCGCGTCC TCGTGTCCTT GCACGCTCCG GCGCGGGCGG GGTGGGCAGC
 14501 TCAAAGGCAC GACCGTCAGC GGGGTCTGGT GTGGGAGGAC GATGACTCGG
 AGTTTCCGTG CTGGCAGTCG CCCAGACCA CACCCTCCTG CTACTGAGCC
 14551 CAGACGACAG CAGCGTCTG GATTGGSAG GGAGTGGCAA CCCGTTTGGC
 GTCTGCTGTC GTGCGAGGAC CTAAACCTC CCTCACCCTT GGGCAAACGC
 14601 CACCTTCGCC CCAGGCTGGG GAGAATGTTT TAAAAAATAA AAAAGCATGA
 GTGGAAGCGG GGTCCGACCC CTCTTACAAA ATTTTTTTTT TTTTCGTACT
 14651 TGCAAAATAA AAAACTCACC AAGGCCATGG CACCGAGCGT TGGTTTCTT
 ACGTTTATAT TTTTGAGTGG TTCCGGTACC GTGGCTCGCA ACCAAAAGAA
 14701 GTATTCCCTT TAGTATGCGG CGCGCGGCGA TGTATGAGGA AGGTCCTCCT
 CATAAGGGGA ATCATAAGCC GCGCGCCGCT ACATACTCCT TCCAGGAGGA
 14751 CCCTCCTACG AGAGTGTGGT GAGCGCGGCG CCAGTGGCGG CGGCGCTGGG
 GGGAGGATGC TCTCACACCA CTCGCGCCGC GGTCAACCGC GCCGCGACCC
 14801 TTCTCCCTTC GATGCTCCCC TGGACCCGCC GTTTGTGCCT CCGCGGTACC
 AAGAGGGAAG CTACGAGGGG ACCTGGGCGG CAAACACGGA GCGGCCATGG
 14851 TGCGGCCTAC CGGGGGGAGA AACAGCATCC GTTACTCTGA GTTGGCACCC
 ACGCCGGATG GCGCCCTCT TTGTCGTAGG CAATGAGACT CAACCGTGGG
 14901 CTATTCGACA CCACCCGTGT GTACCTGGTG GACAACAAGT CAACGGATGT
 GATAAGCTGT GGTGGGCACA CATGGACCAC CTGTTGTTCA GTTGCTTACA
 14951 GGCATCCCTG AACTACCAGA ACGACCACAG CAACTTTCTG ACCACGGTCA
 CCGTAGGGAC TTGATGGTCT TGCTGGTGTG GTTGAAGAC TGGTGCCAGT
 15001 TTCAAACAA TGACTACAGC CCGGGGGAGG CAAGCACACA GACCATCAAT
 AAGTTTGTG ACTGATGTG GCGCCCTCC GTTCGTGTGT CTGGTAGTTA
 15051 CTTGACGACC GGTGCACTG GGGCGGCGAC CTGAAAACCA TCCTGCATAC
 GAAGTGTG CCAGCGTGAC CCGCGCGCTG GACTTTTGGT AGGACGTATG
 15101 CAACATGCCA AATGTGAACG AGTTCATGTT TACCAATAAG TTTAAGGCGC
 GTTGTACGGT TTACACTTGC TCAAGTACAA ATGGTTATTC AAATCCGCG

Figure 26 P

15151 GGGTGATGGT GCGCTTG CTTACTAAGG ACAATCAGGT GGAGCTA
 CCCACTACCA CAGCGCGAAC GGATGATTCC TGTAGTCCA CCTCGACTTT
 15201 TACGAGTGGG TGGAGTTCAC GCTGCCCAG GCAACTACT CCGAGACCAT
 ATGCTCACCC ACCTCAAGTG CGACGGGCTC CCGTGTATGA GGCTCTGGTA
 15251 GACCATAGAC CTTATGAACA ACGCGATCGT GGAGCACTAC TTGAAAGTGG
 CTGGTATCTG GAATACTTGT TCGCTAGCA CCTCGTGATG AACTTTCACC
 15301 GCAGACAGAA CGGGGTCTG GAAAGCGACA TCGGGGTAAA GTTTGACACC
 CGTCTGTCTT GCCCAAGAC CTTTCGCTGT AGCCCCATTT CAAACTGTGG
 15351 CGCAACTTCA GACTGGGGTT TGACCCCGTC ACTGGTCTTG TCATGCCTGG
 GCGTTGAAGT CTGACCCCAA ACTGGGGCAG TGACCAGAAC AGTACGGACC
 15401 GGTATATACA AACGAAGCCT TCCATCCAGA CATCATTTTG CTGCCAGGAT
 CCATATATGT TTGCTTCGGA AGGTAGGTCT GTAGTAAAC GACGGTCTTA
 15451 GCGGGGTGGA CTTCAACCCAC AGCCGCCTGA GCAACTTGTG GGGCATCCGC
 CGCCCCACCT GAAGTGGGTG TCGGCGGACT CGTTGAACAA CCCGTAGGCG
 15501 AAGCGGCAAC CCTTCCAGGA GGGCTTTAGG ATCACCTACG ATGATCTGGA
 TTCGCCGTTG GGAAGTCCCT CCCGAAATCC TAGTGGATGC TACTAGACCT
 15551 GGGTGGTAAC ATTCCCGCAC TGTGGATGT GGAAGCTTAC CAGGCGAGCT
 CCCACCATTG TAAGGGCGTG ACAACCTACA CCTGCGGATG GTCCGCTCGA
 15601 TGAAAGATGA CACCGAACAG GCGGGGGGTG GCGCAGGCGG CAGCAACAGC
 ACTTCTACT GTGGCTGTG CCGCCCCAC CGCGTCCGC GTCGTGTGCG
 15651 AGTGGCAGCG GCGCGGAAGA GAACTCCAAC GCGGCAGCCG CGGCAATGCA
 TCACCGTCCG CGCGCTTCT CTTGAGGTG CGCCGTCGGC GCCGTTACGT
 15701 GCCGGTGGAG GACATGAACG ATCATGCCAT TCGCGGCGAC ACCTTTGCCA
 CGGCCACCTC CTGTACTTGC TAGTACGGTA AGCGCCGCTG TGGAACGGT
 15751 CACGGGCTGA GGAGAAGCGC GCTGAGGCCG AAGCAGCGGC CGAAGCTGCC
 GTGCCCCACT CCTCTTCGCG CCACTCCGGC TTCGTGCGCG GCTTCGACGG
 15801 GCCCCCGCTG CGCAACCCGA GGTGAGAGA CCTCAGAAGA AACCAGGTGAT
 CGGGGGCGAC GCGTTGGGCT CCAGCTCTTC GGAGTCTTCT TTGGCCACTA
 15851 CAAACCCCTG ACAGAGGACA GCAAGAAACG CAGTTACAAC CTAATAAGCA
 GTTTGGGGAC TGCTCCTGT CGTCTTTGC GTCAATGTTG GATTATTCGT
 15901 ATGACAGCAC CTTACCCAG TACCGCAGCT GGTACCTTGC ATACAACTAC
 TACTGTCTG GAAGTGGGTC ATGGCGTCGA CCATGGAACG TATGTTGATG
 15951 GCGCACCTC AGACCGGAAT CCGCTCATGG ACCCTGCTTT GCACTCCTGA
 CCGCTGGGAG TCTGGCCTTA GCGAGTACC TGGGACGAAA CGTGAGGACT
 16001 CGTAACCTGC GGCTCGGAGC AGGTCTACTG GTCGTTGCCA GACATGATGC
 GCATTGGACG CCGAGCCTCG TCCAGATGAC CAGCAACGGT CTGTACTACG
 16051 AAGACCCCGT GACCTTCCGC TCCACGCGCC AGATCAGCAA CTTTCCGGTG
 TTCTGGGGCA CTGGAAGGCG AGGTGCGCGG TCTAGTCGTT GAAAGGCCAC

Figure 26 A

16101 GTGGGCGCGC A TGGTTGCC CGTGCCTCC AAGAGCTTCT ACAACGCTCA
 CACCCGCGGC TACAACGG GCACGTGAGG TTCTCGAAGA TGGTGCCTGT
 16151 GGCCGTCTAC TCCCAACTCA TCCGCCAGTT TACCTCTCTG ACCCACGTGT
 CCGGCAGATG AGGGTTGAGT AGGCGGTCAA ATGGAGAGAC TGGGTGCACA
 16201 TCAATCGCTT TCCCGAGAAC CAGATTTTGG CGCGCCCGCC AGCCCCCACC
 AGTTAGCGAA AGGGCTCTTG GTCTAAAACC GCGCGGGCGG TCGGGGGTGG
 16251 ATCACCACCG TCAGTGAAAA CGTTCCCTGCT CTCACAGATC ACGGGACGCT
 TAGTGGTGGC AGTCACTTTT GCAAGGACGA GAGTGTCTAG TGCCCTGCGA
 16301 ACCGCTGCGC AACAGCATCG GAGGAGTCCA GCGAGTGACC ATTACTGACG
 TGGCGACGCG TTGTCTAGC CTCTCAGGT CGCTCACTGG TAATGACTGC
 16351 CCAGACGCGC CACCTGCCCC TACGTTTACA AGGCCCTGGG CATAGTCTCG
 GGTCTGCGGC GTGGACGGGG ATGCAAATGT TCCGGGACCC GTATCAGAGC
 16401 CCGCGCGTCC TATCGAGCCG CACTTTTGA GCAAGCATGT CCATCCTTAT
 GCGCGCAGG ATAGCTCGGC GTGAAAACT CGTTCGTACA GGTAGGAATA
 16451 ATCGCCACAG AATAACACAG GCTGGGGCCT GCGCTTCCCA AGCAAGATGT
 TAGCGGGTCG TTATTGTGTC CGACCCCGGA CGCGAAGGGT TCGTTCTACA
 16501 TTGGCGGGGC CAAGAAGCGC TCCGACCAAC ACCCAGTGCG CGTGCGCGGG
 AACCGCCCCG GTTCTTCGCG AGGCTGGTGG TGGGTACGCG GCACGCGCCC
 16551 CACTACCGCG CGCCCTGGGG CGCGCACAAA CGCGGCCGCA CTGGGCGCAC
 GTGATGGCGC GCGGGACCCC GCGCGTGTTC GCGCCGCGT GACCCGCGTG
 16601 CACCGTCGAT GACGCCATCG ACGCGGTGGT GGAGGAGCG CGCAACTACA
 GTGGCAGCTA CTGCGGTAGC TCGCCACCA CCTCTCCGC GCGTTGATGT
 16651 CGCCACGCC GCCACAGTG TCCACAGTGG ACGCGGCCAT TCAGACCGTG
 GCGGGTGGG GGTGGTAC AGGTGTCACC TCGCCGCGTA AGTCTGGCAC
 16701 GTGCGCGGAG CCCGGCGCTA TGCTAAAATG AAGAGACGGC GGAGGCGCGT
 CACGCGCCTC GGGCCGCGAT ACGATTTTAC TTCTCTGCCG CCTCCGCGCA
 16751 AGCACGTGCG CACCGCCGCC GACCCGGCAC TGCCGCCCAA CGCGCGGCGG
 TCGTGACGCG GTGGCGGCGG CTGGGCCGTG ACGCGGGGT GCGCGCCGCC
 16801 CGGCCCTGCT TAACCGCGCA CGTCGCACCG GCCGACGGG GGCATGCGG
 GCCGGGACGA ATTGGCGCGT GCAGCGTGGC CGGCTGCCCC CCGGTACGCC
 16851 GCCGCTCGAA GGCTGGCCGC GGGTATTGTC ACTGTGCCCC CCAGGTCCAG
 CGGCGAGCTT CCGACCGCGC CCCATAACAG TGACACGGGG GTCCAGGTG
 16901 GCGACGAGCG GCCGCCGCG CAGCCGCGGC CATTAGTGCT ATGACTCAGG
 CGCTGCTCGC CGGCGGCGTC GTCGGCGCGG GTAATCACGA TACTGAGTCC
 16951 GTCGACGGGG CAACGTGTAT TGGGTGCGCG ACTCGGTTAG CGGCCTGCGC
 CAGCGTCCCC GTTGACATA ACCCACGCGC TGAGCCAATC GCCGGACGCG
 17001 GTGCCCCGTC GCACCCGCC CCCGCGCAAC TAGATTGCAA GAAAAACTA
 CACGGGCACG CGTGGGCGGG GGGCGCGTTG ATCTAACGTT CTTTTTGTAT

Figure 26 R

17051 CTTAGACTCG TTTGTTGTA TGTATCCAGC GCGGGCGGCG CCGAACTG
 GAATCTGAGC ATGACAACAT ACATAGGTCT CCGCCGCCGC GCGTTGCTTC
 17101 CTATGTCCAA GCGCAAAATC AAAGAAGAGA TGCTCCAGGT CATCGCGCCG
 GATACAGGTT CCGGTTTTAG TTTCTTCTCT ACGAGGTCCA GTAGCGCGGC
 17151 GAGATCTATG GCGCCCCGAA GAAGGAAGAG CAGGATTACA AGCCCCGAAA
 CTCTAGATAC CCGGGGGCTT CTTCTTCTCT GTCCTAATGT TCGGGGCTTT
 17201 GCTAAAGCGG GTCAAAAAGA AAAAGAAAGA TGATGATGAT GAACTTGACG
 CGATTTCCGC CAGTTTTTCT TTTCTTTCT ACTACTACTA CTGGAACGTC
 17251 ACGAGGTGGA ACTGCTGCAC GCTACCGCGC CCAGGCGACG GGTACAGTGG
 TGCTCCACCT TGACGACGTG CGATGGCGCG GGTCCGCTGC CCATGTCACC
 17301 AAAGGTCGAC GCGTAAACG TGTTTTGCGA CCCGGCACCA CCGTAGTCTT
 TTTCCAGCTG CGCATTTTGC ACAAACGCT GGGCCGTGGT GGCATCAGAA
 17351 TACGCCCCGT GAGCGCTCCA CCCGCACCTA CAAGCGCGTG TATGATGAGG
 ATCGGGGCA CTCGCGAGGT GGGCGTGGAT GTTCGCGCAC ATACTACTCC
 17401 TGTCAGGCGA CGAGGACCTG CTTGAGCAGG CCAACGAGCG CCTCGGGGAG
 ACATGCCGCT GCTCCTGGAC GAACTCGTCC GGTGCTCGC GGAGCCCCTC
 17451 TTTGCCTACG GAAAGCGGCA TAAGGACATG CTGGCGTTGC CGCTGGACGA
 AAACGGATGC CTTTCGCCGT ATTCTGTAC GACCGCAACG GCGACCTGCT
 17501 GGGCAACCCA ACACCTAGCC TAAAGCCCGT AACACTGCAG CAGGTGCTGC
 CCCGTTGGGT TGTGGATCGG ATTCGGGCA TTGTGACGTC GTCCACGACG
 17551 CCGCGCTTGC ACCGTCCGAA GAAAAGCGCG GCCTAAAGCG CGAGTCTGGT
 GGCGCGAACG TGGCAGGCTT CTTTCGCGC CGGATTTGCG GCTCAGACCA
 17601 GACTTGGCAC CCACCGTGCA GCTGATGGTA CCCAAGCGCC AGCGACTGGA
 CTGAACCGTG GGTGGCACGT CGACTACCAT GGGTTCGCGG TCGCTGACCT
 17651 AGATGTCTTG GAAAAAATGA CCGTGGAACC TGGGCTGGAG CCCGAGGTCC
 TCTACAGAAC CTTTTTTACT GGCACCTTGG ACCCGACCTC GGGCTCCAGG
 17701 GCGTGCGGCC AATCAAGCAG GTGGCGCCCG GACTGGGCGT GCAGACCGTG
 CGCACGCCCG TTAGTTCGTC CACCGCGGCC CTGACCCGCA CGTCTGGCAC
 17751 GACGTTGAGA TACCCACTAC CAGTAGCACC AGTATTGCCA CCGCCACAGA
 CTGCAAGTCT ATGGGTGATG GTCATCGTGG TCATAACGGT GCGGTGTCT
 17801 GGGCATGGAG ACACAAACGT CCCCGGTTGC CTCAGCGGTG GCGGATGCCG
 CCCGTACCTC TGTGTTTCCA GGGGCCAACG GAGTCGCCAC CGCTACGGC
 17851 CCGTGCAGGC GGTGCTGCG GCGCGCTCCA AGACCTCTAC GGAGGTGCAA
 GCCACGTCCG CCAGCGACGC CCGCGCAGGT TCTGGAGATG CCTCCACGTT
 17901 ACGGACCCGT GGATGTTTCG CGTTTCAGCC CCCCGCGGCC CGCGCCGTTT
 TGCTGGGCA CCTACAAAGC GCAAAGTCGG GGGGCCGCGG GCGCGGCAAG
 17951 GAGGAAGTAC GCGCCGCCA GCGCGCTACT GCGCGAATAT GCCCTACATC
 CTCCTTCATG CCGCGGCGGT CCGCGGATGA CCGGCTTATA GGGGATGTAG

Figure 265

18001 CTTCCATTGC GCTACCCCC GGCTATCGTG GCTACACCTA CCGCCCGAGA
 GAAGGTAACG ATGGGGG CCGATAGCAC CGATGTGGAT GGCGGG T
 18051 AGACGAGCAA CTACCCGACG CCGAACCACC ACTGGAACCC GCCGCCGCCG
 TCTGCTCGTT GATGGGCTGC GGCTTGGTGG TGACCTTGGG CGCGCGCGGC
 18101 TCGCCGTGCG CAGCCCGTGC TGGCCCCGAT TTCCGTGCGC AGGGTGGCTC
 AGCGGCAGCG GTCGGGCACG ACCGGGGCTA AAGGCACGCG TCCCACCGAG
 18151 GCGAAGGAGG CAGGACCCTG GTGCTGCCAA CAGCGCGCTA CCACCCAGC
 CGCTTCCTCC GTCTGGGAC CACGACGGTT GTCGCGCGAT GGTGGGGTGC
 18201 ATCGTTTAAA AGCCGGTCTT TGTGGTTCTT GCAGATATGG CCTCACCTG
 TAGCAAATTT TCGGCCAGAA ACACCAAGAA CGTCTATACC GGGAGTGGAC
 18251 CCGCCTCCGT TTCCCGGTGC CGGGATTCCG AGGAAGAATG CACCGTAGGA
 GCGCGAGGCA AAGGGCCACG GCCCTAAGGC TCCTTCTTAC GTGGCATCCT
 18301 GGGGCATGCG CGGCCACGGC CTGACGGGCG GCATGCGTGC TGGCACCAC
 CCCGTACCG GCCGGTGCCG GACTGCCCCG CGTACGCAGC ACGCGTGGTG
 18351 CGCGCGCGGC GCGCGTCGCA CCGTCGCATG CGCGGCGGTA TCCTGCCCT
 GCCCGCCCG CGCGCAGCGT GGCAGCGTAC GCGCCGCCAT AGGACGGGGA
 18401 CCTTATTCCA CTGATCGCCG CGGCGATTGG CGCCGTGCCC GGAATTGCAT
 GGAATAAGGT GACTAGCGGC GCCGCTAACC GCGGCACGGG CCTTAACGTA
 18451 CCGTGGCCTT GCAGGCGCAG AGACACTGAT TAAAAACAAG TTGCATGTGG
 GGCACCGGAA CGTCCGCGTC TCTGTGACTA ATTTTGTTC AACGTACACC
 18501 AAAAAATCAA ATAAAAAGTC TGGACTCTCA CGCTCGCTTG GTCCTGTAAC
 TTTTATAGTT TATTTTTCAG ACCTGAGAGT GCGAGCGAAC CAGGACATTG
 18551 TATTTGTAG AATGGAAGAC ATCAACTTTG CGTCTCTGGC CCCGCGACAC
 ATAAAAACATC TTACCTTCTG TAGTTGAAAC GCAGAGACCG GGGCGCTGTG
 18601 GGCTCGCGCC CGTTCATGGG AACTGGCAA GATATCGGCA CCAGCAATAT
 CCGAGCGCGG GCAAGTACCC TTTGACCGTT CTATAGCCGT GGTGTTATA
 18651 GAGCGGTGGC GCCTTCAGCT GGGGCTCGCT GTGGAGCGGC ATTAAAAATT
 CTCGCCACCG CGGAAGTCGA CCCCAGCGCA CACCTCGCCG TAATTTTAA
 18701 TCGGTTCAC CGTTAAGAAC TATGGCAGGA AGGCCTGGAA CAGCAGCACA
 AGCCAAGGTG GCAATTCTTG ATACCGTCGT TCCGGACCTT GTCGTCGTGT
 18751 GGCCAGATGC TGAGGGATAA GTTGAAAGAG CAAAATTTCC AACAAAAGGT
 CCGGTCTACG ACTCCCTATT CAACTTTCTC GTTTTAAAGG TTGTTTCCA
 18801 GGTAGATGGC CTGGCCTCTG GCATTAGCGG GGTGGTGGAC CTGGCCAACC
 CCATCTACCG GACCGGAGAC CGTAATCGCC CCACCACCTG GACCGGTTGG
 18851 AGGCAGTGCA AAATAAGATT AACAGTAAGC TTGATCCCCG CCCTCCCGTA
 TCCGTCACGT TTTATTCTAA TTGTCATTG AACTAGGGGC GGGAGGGCAT
 18901 GAGGAGCCTC CACCGGCCGT GGAGACAGTG TCTCCAGAGG GCGGTGGCGA
 CTCCTCGGAG GTGGCCGGCA CCTCTGTAC AGAGGTCTCC CCGCACCGCT

Figure 26T

18951 AAAGCGTCCG C●CCGACA GGAAGAAAC TCTGGTGACG CAAATAC●G
 TTTCGCAGGC G●GGGCTGT CCTTCTTTG AGACCACTGC GTTTATC●G

19001 AGCCTCCCTC GTACGAGGAG GCACTAAAGC AAGGCCTGCC CACCACCCGT
 TCGGAGGGAG CATGCTCCTC CGTGATTTCG TTCCGGACGG GTGGTGGGCA

19051 CCCATCGCGC CCATGGCTAC CGGAGTGCTG GGCCAGCACA CACCCGTAAC
 GGGTAGCGCG GGTACCGATG GCCTCACGAC CCGGTCGTGT GTGGGCATTG

19101 GCTGGACCTG CCTCCCCCG CCGACACCCA GCAGAAACCT GTGCTGCCAG
 CGACCTGGAC GGAGGGGGGC GGCTGTGGGT CGTCTTTGGA CACGACGGTC

19151 GCCCGACCGC CGTTGTTGTA ACCCGTCCTA GCCGCGCGTC CCTGCGCCGC
 CGGGCTGGCG GCAACAACAT TGGGCAGGAT CGGCGCGCAG GGACGCGGCG

19201 GCCGCCAGCG GTCCGCGATC GTTGCGGCCC GTAGCCAGTG GCAACTGGCA
 CGGCGGTGCG CAGGCGCTAG CAACGCCGGG CATCGGTAC CGTTGACCGT

19251 AAGCACACTG AACAGCATCG TGGGTCTGGG GGTGCAATCC CTGAAGCGCC
 TTCGTGTGAC TTGTGCTAGC ACCCAGACCC CCACGTTAGG GACTTCGCGG

19301 GACGATGCTT CTGATAGCTA ACGTGTCGTA TGTGTGTCAT GTATGCGTCC
 CTGTACGAA GACTATCGAT TGCACAGCAT ACACACAGTA CATACGCAGG

19351 ATGTGCGCGC CAGAGGAGCT GCTGAGCCGC CGCGCGCCCG CTTTCCAAGA
 TACAGCGGCG GTCTCCTCGA CGACTCGGCG GCAGCGGGCG GAAAGGTTCT

19401 TGGCTACCCC TTCGATGATG CCGCAGTGGT CTTACATGCA CATCTCGGGC
 ACCGATGGGG AAGCTACTAC GGCGTCACCA GAATGTACGT GTAGAGCCCCG

19451 CAGGACGCCT CGGAGTACCT GAGCCCCGGG CTGGTGCACT TTGCCCCGCG
 GTCTGCGGA GCCTCATGGA CTCGGGGCCC GACCACGTCA AACGGGCGCG

19501 CACCGAGACG TACTTCAGCC TGAATAACAA GTTTAGAAAC CCCACGGTGG
 GTGGCTCTGC ATGAAGTCGG ACTTATTGTT CAAATCTTTG GGGTGCCACC

19551 CGCCTACGCA CGACGTGACC ACAGACCGGT CCCAGCGTTT GACGCTGCGG
 GCGGATGCGT GCTGCACTGG TGTCTGGCCA GGGTCGCAA CTGCGACGCC

19601 TTCATCCCTG TGGACCGTGA GGATACTGCG TACTCGTACA AGGCGCGGTT
 AAGTAGGGAC ACCTGGCACT CCTATGACGC ATGAGCATGT TCCGCGCCAA

19651 CACCCTAGCT GTGGGTGATA ACCGTGTGCT GGACATGGCT TCCACGTACT
 GTGGGATCGA CACCCACTAT TGGCACACGA CCTGTACCGA AGGTGCATGA

19701 TTGACATCCG CGGCGTGCTG GACAGGGGCC CTACTTTTAA GCCCTACTCT
 AACTGTAGGC GCCGCACGAC CTGTCCCCGG GATGAAAATT CGGGATGAGA

19751 GGCACGCTCT ACAACGCCCT GGCTCCCAAG GGTGCCCCAA ATCCTTGCGA
 CCGTGACGGA TGTGCGGGA CCGAGGGTTC CCACGGGGTT TAGGAACGCT

19801 ATGGGATGAA GCTGCTACTG CTCTTGAAAT AAACCTAGAA GAAGAGGACG
 TACCCTACTT CGACGATGAC GAGAACTTTA TTTGGATCTT CTTCTCCTGC

19851 ATGACPAACG AGACGAAGTA GACGAGCAAG CTGAGCAGCA AAAAACTCAC
 TACTGTTGCT TCTGCTTCAT CTGCTCGTTC GACTCGTCGT TTTTGTAGTG

Figure 26 u

19901 GTATTGGGC A GCCTTA TTCTGGTATA AATATTACAA AGGAGG T
CATAAACCCG TCCGCGGAAT AAGACCATAT TTATAATGTT TCCTCCCTA

19951 TCAAATAGGT GTCGAAGGTC AAACACCTAA ATATGCCGAT AAAACATTTTC
AGTTTATCCA CAGCTTCCAG TTTGTGGATT TATACGGCTA TTTTGTAAAG

20001 AACCTGAACC TCAAATAGGA GAATCTCAGT GGTACGAAAC AGAAATTAAT
TTGGACTTGG AGTTTATCCT CTTAGAGTCA CCATGCTTTG TCTTTAATTA

20051 CATGCAGCTG GGAGAGTCCT AAAAAAGACT ACCCCAATGA AACCATGTTA
GTACGTGAC CCTCTCAGGA TTTTTTCTGA TGGGGTACT TGGGTACAAT

20101 CGGTTTCATAT GCAAAACCCA CAAATGAAA TGGAGGGCAA GGCATTCTTG
GCCAAGTATA CGTTTTGGGT GTTTACTTTT ACCTCCCGTT CCGTAAGAAC

20151 TAAAGCAACA AAATGGAAG CTAGAAAGTC AAGTGGAAAT GCAATTTTTC
ATTTTCGTTGT TTTACCTTTC GATCTTTCAG TTCACCTTTA CGTTAAAAAG

20201 TCAACTACTG AGGCAGCCGC AGGCAATGGT GATAACTTGA CTCCTAAAGT
AGTTGATGAC TCCGTCCGGC TCCGTTACCA CTATTGAACT GAGGATTTC

20251 GGTATTGTAC AGTGAAGATG TAGATATAGA AACCCAGAC ACTCATATTT
CCATAACATG TCACCTCTAC ATCTATATCT TTGGGGTCTG TGAGTATAAA

20301 CTTACATGCC CACTATTAAG GAAGGTAAC CACGAGAACT AATGGGCCAA
GAATGTACGG GTGATAATTC CTTCCATTGA GTGCTCTTGA TTACCCGGTT

20351 CAATCTATGC CCAACAGGCC TAATTACATT GCTTTTAGGG ACAATTTTAT
GTTAGATACG GGTGTCCGG ATTAATGTAA CGAAAATCCC TGTTAAATA

20401 TGGTCTAATG TATTACAACA GCACGGGTAA TATGGGTGTT CTGGCGGGCC
ACCAGATTAC ATAATGTTGT CGTGCCCAT ATACCCACAA GACCGCCCGG

20451 AAGCATCGCA GTTGAATGCT GTTGTAGATT TGCAAGACAG AAACACAGAG
TTCTAGCGT CAACTTACGA CAACATCTAA ACGTTCTGTC TTTGTGTCTC

20501 CTTTCATACC AGCTTTTGCT TGATTCCATT GGTGATAGAA CCAGGTACTT
GAAAGTATGG TCGAAAACGA ACTAAGGTAA CCACTATCTT GGTCCATGAA

20551 TTCTATGTGG AATCAGGCTG TTGACAGCTA TGATCCAGAT GTTAGAATTA
AAGATACACC TTAGTCCGAC AACTGTGAT ACTAGGTCTA CAATCTTAAT

20601 TTGAAAATCA TGGAAGTAA GATGAACTTC CAAATTACTG CTTTCCACTG
AACTTTTAGT ACCTTGACTT CTAATTGAAG GTTTAATGAC GAAAGGTGAC

20651 GGAGGTGTGA TTAATACAGA GACTCTTACC AAGGTAAAC CTAAACAGG
CCTCCACACT AATTATGTCT CTGAGAATGG TTCCATTTTG GATTTTGTCC

20701 TCAGGAAAAT GGATGGGAAA AAGATGCTAC AGAATTTTCA GATAAAAATG
AGTCTTTTTA CCTACCCTTT TTCTACGATG TCTTAAAAGT CTATTTTAC

20751 AAATAAGAGT TGGAAATAAT TTTGCCATGG AAATCAATCT AAATGCCAAC
TTTATCTCA ACCTTTATTA AAACGGTACC TTTAGTTAGA TTTACGGTTG

20801 CTGTGGAGAA ATTTCTGTG CTCCAACATA GCGCTGTATT TGCCCGACAA
GACACCTCTT TAAAGGACAT GAGGTGTAT CGCGACATAA ACGGGCTGTT

Figure 26 v

20851 GCTAAAGTAC AGCTCTTCCA ACGTAAAAAT TTCTGATAAC CCAAACTTTT
 CGATTTCATG TCGGAAGGT TGCATTTTAA AAGACTATTG GGTTCGCTAA
 20901 ACGACTACAT GAACAAGCGA GTGGTGGCTC CCGGGCTAGT GGAAGTGTAC
 TGCTGATGTA CTGTTCGCT CACCACCGAG GGCCCGATCA CCTGACGATG
 20951 ATTAACCTTG GAGCACGCTG GTCCCTTGAC TATATGGACA ACGTCAACCC
 TAATTGGAAC CTCGTGCGAC CAGGGAACTG ATATACCTGT TGCAGTTGGG
 21001 ATTTAACCAC CACCGCAATG CTGGCCTGCG CTACCGCTCA ATGTTGCTGG
 TAAATGGTG GTGGCGTTAC GACCGGACGC GATGGCGAGT TACAACGACC
 21051 GCAATGGTCG CTATGTGCCC TTCCACATCC AGGTGCCTCA GAAGTTCTTT
 CGTTACCAGC GATACACGGG AAGGTGTAGG TCCACGGAGT CTTCAAGAAA
 21101 GCCATTAAAA ACCTCCTTCT CCTGCCGGGC TCATACACCT ACGAGTGGAA
 CGGTAATTTT TGGAGGAAGA GGACGGCCCG AGTATGTGGA TGCTCACCTT
 21151 CTTCAGGAAG GATGTTAACA TGTTTCTGCA GAGCTCCCTA GGAAATGACC
 GAAGTCCTTC CTACAATTGT ACCAAGACGT CTCGAGGGAT CCTTTACTGG
 21201 TAAGGGTTGA CGGAGCCAGC ATTAAGTTTG ATAGCATTTG CCTTTACGCC
 ATTCCCAACT GCCTCGGTG TAATTCAAAC TATCGTAAAC GGAAATGCGG
 21251 ACCTTCTTCC CCATGGCCCA CAACACCGCC TCCACGCTTG AGGCCATGCT
 TGAAGAAGG GGTACCGGT GTGTGGCGG AGGTGCGAAC TCCGGTACGA
 21301 TAGAAACGAC ACCAACGACC AGTCCTTTAA CGACTATCTC TCCGCCGCCA
 ATCTTTGCTG TGGTTGCTGG TCAGGAAATT GCTGATAGAG AGCGGCGGT
 21351 ACATGCTCTA CCCTATACCC GCCAACGCTA CCAACGTGCC CATATCCATC
 TGTACGAGAT GGGATATGGG CGGTTGCGAT GGTTCACGG GTATAGGTAG
 21401 CCCTCCCGCA ACTGGGCGGC TTCCGCGGC TGGGCCTTCA CGCGCCTTAA
 GGGAGGGCGT TGACCCGCGG AAAGGCGCGG ACCCGGAAGT GCGCGGAATT
 21451 GACTAAGGAA ACCCCATCAC TGGGCTCGGG CTACGACCCT TATTACCTT
 CTGATTCCTT TGGGGTAGTG ACCCGAGCCC GATGCTGGGA ATAATGTGGA
 21501 ACTCTGGCTC TATACCCTAC CTAGATGGAA CCTTTTACCT CAACCACACC
 TGAGACCGAG ATATGGGATG GATCTACCTT GGAAAATGGA GTTGGTGTGG
 21551 TTTAAGAAGG TGGCCATTAC CTTTGACTCT TCTGTCAGCT GGCCTGGCAA
 AAATCTTCC ACCGGTAATG GAAACTGAGA AGACAGTCGA CCGGACCGTT
 21601 TGACCGCTG CTTACCCCA ACGAGTTTGA AATTAAGCGC TCAGTTGACG
 ACTGGCGGAC GAATGGGGGT TGCTCAAACT TTAATTGCGG AGTCAACTGC
 21651 GGGAGGGTTA CAACGTTGCC CAGTGTAACA TGACCAAAGA CTGGTTCCTG
 CCTCCCAAT GTTGAACGG GTCACATTGT ACTGGTTTCT GACCAAGGAC
 21701 GTACAAATGC TAGCTAATA TAACATTGGC TACCAGGGCT TCTATATCCC
 CATGTTTACG ATCGATTGAT ATTGTAACCG ATGGTCCCGA AGATATAGGG
 21751 AGAGAGCTAC AAGGACCGCA TGTACTCCTT CTTTAGAAAC TTCCAGCCCA
 TCTCTCGATG TTCCTGGCGT ACATGAGGAA GAAATCTTTG AAGGTGGGT

Figure 26 W

21801 TGAGCCGTCA GCTGGTGGAT GATACTAAAT ACAAGGACTA CCAACACCTG
 ACTCGGCAGT CACCTA CTATGATTTA TGTTCCTGAT GGTGT AC
 21851 GGCATCTAC ACCAACACAA CAACTCTGGA TTTGTTGGCT ACCTTGCCCC
 CCGTAGGATG TGGTTGTGTT GTTGAACCT AAACAACCGA TGAACGGGG
 21901 CACCATGCGC GAAGGACAGG CCTACCCTGC TAACTTCCCC TATCCGCTTA
 GTGGTACGCG CTTCTGTCC GGATGGGACG ATTGAAGGGG ATAGGCCAAT
 21951 TAGGCAAGAC CGCAGTTGAC AGCATTACCC AGAAAAAGTT TCTTTGCGAT
 ATCCGTTCTG GCGTCAACTG TCGTAATGGG TCTTTTCAA AGAAACGCTA
 22001 CGCACCCCTTT GCGCATCCC ATTCTCCAGT AACTTTATGT CCATGGGCGC
 CCGTGGGAAA CCGCGTAGGG TAAGAGGTCA TTGAATACA GGTACCCGCG
 22051 ACTCACAGAC CTGGGCCAAA ACCTTCTCTA CGCCAATCC GCCACGCGC
 TGAGTGTCTG GACCCGGTTT TGAAGAGAT GCGTTGAGG CGGGTGCGCG
 22101 TAGACATGAC TTTTGAGGTG GATCCCATGG ACGAGCCAC CCTTCTTTAT
 ATCTGTACTG AAACTCCAC CTAGGTACC TGCTCGGGTG GGAAGAAATA
 22151 GTTTTGTGTTG AAGTCTTTGA CGTGGTCCGT GTGCACCAGC CGCACGCGG
 CAAAACAAAC TTCAGAACT GCACCAGGCA CACGTGGTCG CCGTGGCGCC
 22201 CGTCATCGAA ACCGTGTACC TGCACAGCC CTTCTCGGCC GGCAACGCCA
 GCAGTAGCTT TGGCACATGG ACGCGTGGG GAAGAGCCGG CCGTTGCGGT
 22251 CAACATAAAG AAGCAAGCAA CATCAACAAC AGCTGCCGCC ATGGGCTCCA
 GTGTATTTC TTCGTTTCGT GTAGTTGTTG TCGACGGCGG TACCCGAGGT
 22301 GTGAGCAGGA ACTGAAAGCC ATTGTCAAAG ATCTTGTTG TGGGCCATAT
 CACTCGTCCT TGACTTTCGG TAACAGTTTC TAGAACCAAC ACCCGGTATA
 22351 TTTTGGGCA CCTATGACAA GCGCTTTCCA GGCTTTGTTT CTCCACACAA
 AAAAACCCTT GGATACTGTT CCGGAAAGGT CCGAAACAA GAGGTGTGTT
 22401 GCTCGCCTGC GCCATAGTCA ATACGGCCCG TCGCGAGACT GGGGCGGTAC
 CGAGCGGACG CCGTATCAGT TATGCCGCC AGCGCTCTGA CCCCCGATG
 22451 ACTGGATGGC CTTTGCCCTG AACC CGCACT CAAAACATG CTACCTCTTT
 TGACCTACCG GAAACGGACC TTGGGCGTGA GTTTTGTAC GATGAGAAA
 22501 GAGCCCTTTG GCTTTTCTGA CCAGCGACTC AAGCAGGTTT ACCAGTTTGA
 CTCGGGAAAC CGAAAAGACT GGTGCTGAG TTCGTCCAA TGGTCAAAC
 22551 GTACGAGTCA CTCCTGCGCC GTAGCGCCAT TGCTTCTCC CCCGACCGCT
 CATGCTCAGT GAGGACGCGG CATCGCGGTA ACGAAGAAGG GGGCTGGCGA
 22601 GTATAACGCT GGAAGAGTCC ACCCAAAGCG TACAGGGGCC CAACTCGGCC
 CATATTGCGA CCTTTTCAGG TGGGTTTCGC ATGTCCCCG GTTGAGCCGG
 22651 GCCTGTGGAC TATTCTGCTG CATGTTTCTC CACGCCTTG CCAACTGGCC
 CGGACACCTG ATAAGACGAC GTACAAAGAG GTGCGGAAAC GGTGACCGG
 22701 CCAAACCTCC ATGGATCACA ACCCCACCAT GAACCTTATT ACCGGGGTAC
 GGTGAGGG TACCTAGTGT TGGGGTGTA CTTGGAATAA TGGCCCCATG

Figure 26 X

22751 CCAACTCCAT GCTCAACAGT CCCCAGGTAC AGCCCACCGT CCGTGGGAC
 GGTTCAGGTA CTTGTGCA GGGGTCCATG TCGGGTGGGA CGCAGC
 22801 CAGGAACAGC TCTACAGCTT CCTGGAGCGC CACTCGCCCT ACTTCCGCAG
 GTCCTTGTCG AGATGTCGAA GGACCTCGCG GTGAGCGGGA TGAAGGCGTC
 22851 CCACAGTGCG CAGATTAGGA GCGCCACTTC TTTTGTGCAC TTGAAAAACA
 GGTGTACGCG GTCTAATCCT CGCGGTGAAG AAAACAGTG AACTTTTGT
 22901 TGTAATAATA ATGTACTAGA GACACTTTCA ATAAAGGCAA ATGCTTTTAT
 ACATTTTAT TACATGATCT CTGTGAAAGT TATTCCGTT TACGAAAAATA
 22951 TTGTACACTC TCGGGTGATT ATTTACCCCC ACCCTTGCCG TCTGCGCCGT
 AACATGTGAG AGCCCACTAA TAAATGGGGG TGGGAACGGC AGACGCGGCA
 23001 TTAAAAATCA AAGGGGTTCT GCCGCGCATC GCTATGCGCC ACTGGCAGGG
 AATTTTGTAGT TTCCCAAGA CGGCGCGTAG CGATACGCGG TGACCGTCCC
 23051 ACACGTTGCG ATACTGGTGT TTAGTGCTCC ACTTAAACTC AGGCACAACC
 TGTGCAACGC TATGACCACA AATCAGAGG TGAATTGAG TCCGTGTTGG
 23101 ATCCGCGGCA GCTCGGTGAA GTTTTCACTC CACAGGCTGC GCACCATCAC
 TAGGCGCCGT CGAGCCACTT CAAAAGTGAG GTGTCCGACG CGTGGTAGTG
 23151 CAACGCGTTT AGCAGGTGCG GCGCCGATAT CTTGAAGTCG CAGTTGGGGC
 GTTGCGCAAA TCGTCCAGCC CGCGGCTATA GAACTTCAGC GTCAACCCCG
 23201 CTCCGCCCTG CGCGCGCGAG TTGCGATACA CAGGGTTGCA GCACTGGAAC
 GAGCGGGGAC GCGCGCGCTC AACGCTATGT GTCCCAACGT CGTGACCTTG
 23251 ACTATCAGCG CCGGGTGGTG CACGCTGGCC AGCACGCTCT TGTGCGAGAT
 TGATAGTCGC GGCCACCAC GTGCGACCGG TCGTGCAGA ACAGCCTCTA
 23301 CAGATCCGCG TCCAGGTCCT CCGCGTTGCT CAGGGCGAAC GGAGTCAACT
 GTCTAGGCGC AGGTCCAGGA GGCGCAACGA GTCCCGCTG CCTCAGTTGA
 23351 TTGGTAGCTG CCTTCCAAA AAGGGCGCGT GCCCAGGCTT TGAGTTGCAC
 AACCATCGAC GGAAGGGTTT TTCCCGCGCA CGGGTCCGAA ACTCAACGTG
 23401 TCGCACCGTA GTGGCATCAA AAGGTGACCG TGCCCGGTCT GGGCGTTAGG
 AGCGTGCGAT CACCGTAGTT TTCCACTGCG ACGGGCGAGA CCCGCAATCC
 23451 ATACAGCGCC TGCATAAAAG CCTTGATCTG CTTAAAAGCC ACCTGAGCCT
 TATGTCGCGG ACGTATTTTC GGAAC TAGAC GAATTTTCGG TGGACTCGGA
 23501 TTGCGCCTTC AGAGAAGAAC ATGCCGCAAG ACTTGCCGGA AACTGATTG
 AACCGGGAAG TCTCTTCTTG TACGGCGTTC TGAACGGCCT TTTGACTAAC
 23551 GCCGGACAGG CCGCGTCGTG CACGCAGCAC CTTGCGTCGG TGTGGAGAT
 CGGCCGTGCC GCGCGAGCAC GTGCGTCGTG GAACGCAGCC ACAACCTCTA
 23601 CTGCACCACA TTTCGGCCCC ACCGGTTCTT CACGATCTTG GCCTTGCTAG
 GACGTGGTGT AAAGCCGGGG TGGCCAAGAA GTGCTAGAAC CGGAACGATC
 23651 ACTGCTCCTT CAGCGCGCGC TGCCCGTTTT CGCTCGTCAC ATCCATTTC
 TGACGAGGAA GTCGCGCGCG ACGGGCAAAA GCGAGCAGTG TAGGTAAAGT

Figure 26Y

23701 ATCACGTGCT CATTATTAT CATAATGCTT CCGTGTAGAC ACTTAATTC
TAGTGCACGA GGAATAAATA GTATTACGAA GGCACATCTG TGAATTCGAG

23751 GCCTTCGATC TCAGCGCAGC GGTGCAGCCA CAACGCGCAG CCCGTGGGCT
CGGAAGCTAG AGTCGCGTCG CCACGTCGGT GTTGC GCGTC GGGCACCCGA

23801 CGTGATGCTT GTAGGTCACC TCTGCAAACG ACTGCAGGTA CGCCTGCAGG
GCACTACGAA CATCCAGTGG AGACGTTTGC TGACGTCCAT GCGGACGTCC

23851 AATCGCCCCA TCATCGTCAC AAAGGTCTTG TTGCTGGTGA AGGTCAGCTG
TTAGCGGGGT AGTAGCAGTG TTCCAGAAC AACGACCACT TCCAGTCGAC

23901 CAACCCGCGG TGCTCCTCGT TCAGCCAGGT CTGCATACG GCCGCCAGAG
GTTGGGCGCC ACCAGGAGCA AGTCGGTCCA GAACGTATGC CGGCGGTCTC

23951 CTTCACCTTG GTCAGGCAGT AGTTTGAAGT TCGCCTTTAG ATCGTTATCC
GAAGGTGAAC CAGTCCGTCA TCAAACCTCA AGCGGAAATC TAGCAATAGG

24001 ACGTGGTACT TGTCATCAG CGCGCGCGCA GCCTCCATGC CCTTCTCCCA
TGCACCATGA ACAGGTAGTC GCGCGCGCGT CGGAGGTACG GGAAGAGGGT

24051 CGCAGACACG ATCGGCACAC TCAGCGGGTT CATCACCCTA ATTTCACTTT
GCGTCTGTGC TAGCCGTGTG AGTCGCCCAA GTAGTGGCAT TAAAGTGAAA

24101 CCGCTTCGCT GGGCTCTTCC TCTTCTCTT GCGTCCGCAT ACCACGCGCC
GGCGAAGCGA CCCGAGAAGG AGAAGGAGAA CGCAGGCGTA TGGTGC GCGG

24151 ACTGGGTCTG CTTCATTCAG CCGCGCACT GTGCGCTTAC CTCCTTTGCC
TGACCCAGCA GAAGTAAGTC GCGGCGTGA CACGCGAATG GAGGAAACGG

24201 ATGCTTGATT AGCACCGGTG GGTGCTGAA ACCCACCATT TGATCGCCCA
TACGAACTAA TCGTGGCCAC CCAACGACTT TGGGTGGTAA ACATCGCGGT

24251 CATCTTCTCT TTCTTCTCTG CTGTCCACGA TTACCTCTGG TGATGGCGGG
GTAGAAGAGA AAGAAGGAGC GACAGGTGCT AATGGAGACC ACTACCGCCC

24301 CGCTCGGGCT TGGGAGAAGG GCGCTTCTTT TTCTTCTTGG GCGCAATGGC
GCGAGCCCGA ACCCTCTTCC CCGGAAGAAA AAGAAGAACC CGCGTTACCG

24351 CAAATCCGCC GCCGAGGTG ATGGCCGCGG GCTGGGTGTG CGCGGCACCA
GTTTAGGCGG CGGCTCCAGC TACCGGCGCC CGACCCACAC GCGCCGTGGT

24401 GCGCGTCTTG TGATGAGTCT TCCTCGTCCT CGGACTCGAT ACGCCGCTC
CGCGCAGAAC ACTACTCAGA AGGAGCAGGA GCCTGAGCTA TCGGCGGAG

24451 ATCCGCTTTT TTGGGGGCGC CCGGGGAGCC GCGGCGACG GGGACGGGA
TAGGCGAAAA AACCCCGCGG GGCCCCCTCCG CCGCCGTCTC CCCTGCCCTT

24501 CGACACGTCC TCCATGGTTG GGGGACGTG CGCCGCACCG CGTCCGCGCT
GCTGTGCAGG AGGTACCAAC CCCCTGCAGC GCGGCGTGGC GCAGGCGCGA

24551 CGGGGGTGGT TTCGCGCTGC TCCTCTTCCC GACTGGCCAT TTCCTTCTCC
GCCCCACCA AAGCGCGACG AGGAGAAGGG CTGACCGGTA AAGGAAGAGG

24601 TATAGGCAGA AAAAGATCAT GGAGTCAGTC GAGAAGAAGG ACAGCCTAAC
ATATCCGTCT TTTCTAGTA CCTCAGTCAG CTCTTCTTCC TGTCGGATTG

Figure 262

24651 CGCCCCCTCT GTCGCA CCACCGCTC CACCGATGCC GCAACGTC
GCGGGGGAGA CTCAAGCGGT GGTGGCGGAG GTGGCTACGG CGGTTGCGCG

24701 CTACCACCTT CCCCGTCGAG GCACCCCGC TTGAGGAGGA GGAAGTGATT
GATGGTGGA GGGGCAGCTC CGTGGGGGCG AACTCCTCCT CCTTCACTAA

24751 ATCGAGCAGG ACCCAGGTTT TGTAAGCGAA GACGACGAGG ACCGCTCAGT
TAGCTCGTCC TGGGTCCAAA ACATTGCTT CTGCTGCTCC TGGCGAGTCA

24801 ACCAACAGAG GATAAAAAGC AAGACCAGGA CAACGCAGAG GCAAACGAGG
TGTTTGCTC CTATTTTTCG TTCTGGTCTT GTTGCCTCTC CGTTTGCTCC

24851 AACAAGTCGG GCGGGGGGAC GAAAGGCATG GCGACTACCT AGATGTGGGA
TTGTTACGCC CGCCCCCTG CTTTCCGTAC CGCTGATGGA TCTACACCTT

24901 GACGACGTGC TGTGAAGCA TCTGCAGCGC CAGTGCGCCA TTATCTGCGA
CTGCTGCAGG ACAACTTCGT AGACGTGCGG GTCACGCGGT AATAGACGCT

24951 CGCGTTGCAA GAGCGCAGCG ATGTGCCCTT CGCCATAGCG GATGTCAGCC
GCGCAACGTT CTCGCGTCGC TACACGGGGA GCGGTATCGC CTACAGTCGG

25001 TTGCCTACGA ACGCCACCTA TTCTCACCGC GCGTACCCCC CAAACGCCAA
AACGGATGCT TCGGCTGGAT AAGAGTGGCG CGCATGGGGG GTTTGCGGTT

25051 GAAAACGGCA CATGCGAGCC CAACCCGCGC CTCAACTTCT ACCCCGTATT
CTTTTGCCGT GTACGCTCGG GTTGGGCGCG GAGTTGAAGA TGGGGCATAA

25101 TGCCGTGCCA GAGGTGCTTG CCACCTATCA CATCTTTTTC CAAAACGCA
ACGGCACGGT CTCCACGAAC GGTGGATAGT GTAGAAAAAG GTTTTGACGT

25151 AGATACCCCT ATCCTGCCGT GCCAACCGCA GCCGAGCGGA CAAGCAGCTG
TCTATGGGGA TAGGACGGCA CGGTTGGCGT CGGCTCGCCT GTTCGTCGAC

25201 GCCTTGCGGC AGGGCGCTGT CATACCTGAT ATCGCCTCGC TCAACGAAGT
CGGAACGCCG TCCGCGACA GTATGGACTA TAGCGGAGCG AGTTGCTTCA

25251 GCCAAAAATC TTTGAGGGTC TTGGACGCGA CGAGAAGCGC GCGGCAAACG
CGGTTTTTAG AAACCTCCAG AACCTGCGCT GCTCTTCGCG CGCCGTTTGC

25301 CTCTGCAACA GGAAAACAGC GAAAATGAAA GTCACCTCTGG AGTGTTGGTG
GAGACGTTGT CCTTTTGTG CTTTTACTTT CAGTGAGACC TCACAACCAC

25351 GAACTCGAGG GTGACAACGC GCGCCTAGCC GTACTAAAAC GCAGCATCGA
CTTGAGCTCC CACTGTTGCG CGCGGATCGG CATGATTTTG CGTCGTAGCT

25401 GGTCACCCAC TTTGCCTACC CGGCACCTAA CCTACCCCCC AAGGTCATGA
CCAGTGCGTG AAACGGATGG GCCGTGAATT GGATGGGGGG TTCCAGTACT

25451 GCACAGTCAT GAGTGAGCTG ATCGTGCGCC GTGCGCAGCC CCTGGAGAGG
CGTGTCAGTA CTACTCGAC TAGCACGCGG CACGCGTCGG GGACCTCTCC

25501 GATGCAAATT TGCAAGAACA AACAGAGGAG GGCCTACCCG CAGTTGGCGA
CTACGTTTAA ACGTTCTTGT TTGTCTCTC CCGGATGGGC GTCAACCGCT

25551 CGAGCAGCTA CGCGCTGGC TTCAAACGCG CGAGCCTGCC GACTTGAGG
GCTCGTCGAT CGCGCGACCG AAGTTTGCGC GCTCGGACGG CTGAACCTCC

Figure 26 AA

25601 AGCGACGCAA AATGATG GCCGCACTGC TCGTTACCGT GGAGCTAG
 TCGCTGCGTT TGATTACTAC CCGCGTCACG AGCAATGGCA CCTCGAACTC
 25651 TGCATGCAGC GGTTCCTTGC TGACCCGGAG ATGCAGCGCA AGCTAGAGGA
 ACGTACGTCG CCAAGAAACG ACTGGGCCTC TACGTCGCGT TCGATCTCCT
 25701 AACATTGCAC TACACCTTTC GACAGGGCTA CGTACGCCAG GCCTGCAAGA
 TTGTAACGTG ATGTGGAAG CTGTCCCGAT GCATGCGGTC CGGACGTTCT
 25751 TCTCCAACGT GGAGCTCTGC AACCTGGTCT CCTACCTTGG AATTTTGCAC
 AGAGGTTGCA CCTCGAGACG TTGGACCAGA GGATGGAACC TTAAACGTG
 25801 GAAAACCGCC TTGGGCAAAA CGTGCTTCAT TCCACGCTCA AGGGCGAGGC
 CTTTGGGCGG AACCCGTTTT GCACGAAGTA AGGTGCGAGT TCCCGCTCCG
 25851 GCGCGCGGAC TACGTCCGCG ACTGCGTTTA CTTATTTCTA TGCTACACCT
 CCGCGCGCTG ATGCAGGCGC TGACGCAAT GAATAAGAT ACGATGTGGA
 25901 GGCAGACGGC CATGGGCGTT TGGCAGCAGT GCTTGGAGGA GTGCAACCTC
 CCGTCTGCCG GTACCCGCAA ACCGTCTGCA CGAACCTCCT CACGTTGGAG
 25951 AAGGAGCTGC AGAACTGCT AAAGCAAAC TTGAAGGACC TATGGACGGC
 TTCTCGACG TCTTTGACGA TTTGTTTTG AACTCTCTGG ATACCTGCCG
 26001 CTTCAACGAG CGCTCCGTGG CCGCGCACCT GCGGACATC ATTTTCCCCG
 GAAGTTGCTC GCGAGGCACC GCGCGTGGA CCGCTGTAG TAAAAGGGG
 26051 AACGCCGTGCT TAAAACCTG CAACAGGCTC TGCCAGACTT CACCACTCAA
 TTGCGGACGA ATTTTGGGAC GTTGTCCAG ACGGTCTGAA GTGGTCAGTT
 26101 AGCATGTTGC AGAACTTTAG GAACTTTATC CTAGAGCGCT CAGGAATCTT
 TCGTACAACG TCTTGAAATC CTTGAAATAG GATCTCGCA GTCTTAGAA
 26151 GCGCGCCACC TGCTGTGCAC TTCCTAGCGA CTTTGTGCCC ATTAAGTACC
 CGGGCGGTGG ACGACACGTG AAGGATCGCT GAAACACGGG TAATTCATGG
 26201 GCGAATGCCC TCCGCCGCTT TGGGGCCACT GCTACCTTCT GCAGCTAGCC
 CGCTTACGGG AGGCGGCGAA ACCCGGTGA CGATGGAAGA CGTCGATCGG
 26251 AACTACCTTG CCTACCACTC TGACATAATG GAAGACGTGA GCGGTGACGG
 TTGATGGAAC GGATGGTGAG ACTGTATTAC CTTCTGCACT CGCCACTGCC
 26301 TCTACTGGAG TGTCACGTG GCTGCAACCT ATGCACCCCG CACCGCTCCC
 AGATGACCTC ACAGTGACAG CGACGTGGA TACGTGGGGC GTGGCGAGGG
 26351 TGGTTTGCAA TTCCGAGCTG CTAAACGAAA GTCAAATTAT CGGTACCTTT
 ACCAAACGTT AAGCGTCGAC GAATTGCTTT CAGTTTAATA GCCATGGAAA
 26401 GAGCTGCAGG GTCCCTCGCC TGACGAAAAG TCCGCGGCTC CGGGGTGAA
 CTCGACGTCC CAGGGAGCGG ACTGCTTTTC AGGCGCGAG GCCCAACTT
 26451 ACTCACTCCG GGGCTGTGGA CGTCGGCTTA CCTTCGCAA TTTGTACCTG
 TGAGTGAGGC CCCGACACCT GCAGCCGAAT GGAAGCGTTT AAACATGGAC
 26501 AGGACTACCA CGCCACGAG ATTAGTTCT ACGAAGACCA ATCCCGCCCG
 TCTGATGGT GCGGGTGCTC TAATCCAAGA TGCTTCTGGT TAGGGCGGGC

Figure 26 AB

26551 CCTAATGCCG AATTACCG CTGCGTCATT ACCCAGGGCC ACATTCGG
 GGATTACGCC TCGAATGGCG GACGCAGTAA TGGGTCCCGG TGTAGAACC
 26601 CCAATTGCAA GCCATCAACA AAGCCCGCCA AGAGTTTCTG CTACGAAAGG
 GGTTAACGTT CGGTAGTTGT TTCGGGCGGT TCTCAAAGAC GATGCTTTCC
 26651 GACGGGGGGT TTACTTGGAC CCCCAGTCCG GCGAGGAGCT CAACCCAATC
 CTGCCCCCA AATGAACCTG GGGGTCAGGC CGTCCTCGA GTTGGGTTAG
 26701 CCCCCGCCG CGCAGCCCTA TCAGCAGCAG CCGCGGGCCC TTGCTTCCCA
 GGGGGCGGCG GCGTCGGGAT AGTCGTCGTC GGCGCCCGG AACGAAGGCT
 26751 GGATGGCACC CAAAAGAAG CTGCAGCTGC CGCCGCCACC CACGGACGAG
 CCTACCGTGG GTTTTCTTC GACGTCGACG GCGGCGGTGG GTGCCTGCTC
 26801 GAGGAATACT GGGACAGTCA GGCAGAGGAG GTTTTGGACG AGGAGGAGGA
 CTCCTTATGA CCTGTCACT CCGTCTCCTC CAAAACCTGC TCCTCCTCCT
 26851 GGACATGATG GAAGACTGGG AGAGCCTAGA CGAGGAAGCT TCCGAGGTCTG
 CCTGTACTAC CTTCTGACCC TCTCGGATCT GCTCCTTCGA AGGCTCCAGC
 26901 AAGAGGTGTC AGACGAAACA CCGTCACCCT CGGTCGCAAT CCCCTCGCCG
 TTCTCCACAG TCTGCTTTGT GGCAGTGGGA GCCAGCGTAA GGGGAGCGGC
 26951 GCGCCCCAGA AATCGGCAAC CGGTTCAGC ATGGCTACAA CCTCCGCTCC
 CGCGGGGTCT TTAGCCGTG GCCAAGGTCG TACCGATGTT GGAGGCGAGG
 27001 TCAGGCGCCG CCGGCACTGC CCGTTCGCCG ACCCAACCGT AGATGGGACA
 AGTCCGCGGC GGCCGTGACG GGCAAGCGGC TGGGTTGGCA TCTACCTGT
 27051 CCACTGGAAC CAGGGCCGGT AAGTCCAAGC AGCCGCCGCC GTTAGCCCAA
 GGTGACCTTG GTCCCGGCCA TTCAGGTTCTG TCGGCGGCGG CAATCGGGTT
 27101 GAGCAACAAC AGCGCCAAGG CTACCGCTCA TGGCGCGGGC ACAAGAACGC
 CTCGTTGTTG TCGCGGTTCC GATGGCGAGT ACCGCGCCCG GTTCTTGGC
 27151 CATAGTTGCT TGCITGCAAG ACTGTGGGGG CAACATCTCC TTCGCCCCGC
 GTATCAACGA ACGAACGTTG TGACACCCC GTTGTAGAGG AAGCGGGCGG
 27201 GCTTCTTCT CTACCATCAC GCGGTGGCCT TCCCCGTAA CATCCTGCAT
 CGAAAGAAGA GATGGTAGTG CCGCACCGGA AGGGGGCATT GTAGGACGTA
 27251 TACTACCGTC ATCTCTACAG CCCATACTGC ACCGGCGGCA GCGGCAGCAA
 ATGATGGCAG TAGAGATGTC GGGTATGACG TGGCCGCCGT CGCCGTCGTT
 27301 CAGCAGCGGC CACACAGAAG CAAAGGCGAC CGGATAGCAA GACTCTGACA
 GTCGTCGCCG GTGTGTCTTC GTTCCGCTG GCCTATCGTT CTGAGACTGT
 27351 AAGCCCAAGA AATCCACAGC GCGGCGAGCA GCAGGAGGAG GAGCGCTGCG
 TTCGGGTTCT TTAGGTGTG CCGCGGTGCT CGTCCTCCTC CTCGCGACGC
 27401 TCTGGCGCCC AACGAACCCG TATCGACCCG CGAGCTTAGA AACAGGATTT
 AGACCGCGGG TTGCTTGGGC ATAGCTGGGC GTCGAATCT TTGTCCTAAA
 27451 TTCCCACTCT GTATGCTATA TTTCAACAGA GCAGGGGCCA AGAACAAGAG
 AAGGGTGAGA CATACGATAT AAAGTTGTCT CGTCCCCGGT TCTTGTCTC

Figure 26 AC

27501 CTGAAAATAA A CAGGTC TCTGCGATCC CTCACCCGCA GCTGCC TA
 GACTTTTATT TTTGTCCAG AGACGCTAGG GAGTGGGCGT CGACGGALAT
 27551 TCACAAAAGC GAAGATCAGC TTCGGCGCAC GCTGGAAGAC GCGGAGGCTC
 AGTGTTTTTCG CTTCTAGTCG AAGCCGCGTG CGACCTTCTG CGCCTCCGAG
 27601 TCTTCAGTAA ATACTGCGCG CTGACTCTTA AGGACTAGTT TCGCGCCCTT
 AGAAGTCATT TATGACGCGC GACTGAGAAT TCCTGATCAA AGCGCGGGAA
 27651 TCTCAAATTT AAGCGCGAAA ACTACGTCAT CTCCAGCGGC CACACCCGGC
 AGAGTTTAAA TTCGCGCTTT TGATGCAGTA GAGGTCGCCG GTGTGGGCCG
 27701 GCCAGCACCT GTTGTACGCG CCATTATGAG CAAGGAAATT CCCACGCCCT
 CGGTCTGTGA CAACAGTCGC GGTAACTCTC GTTCCTTTAA GGGTGC GGGA
 27751 ACATGTGGAG TTACCAGCCA CAAATGGGAC TTGCGGCTGG AGCTGCCCAA
 TGACACCTC AATGGTCGGT GTTACCCTG AACGCCGACC TCGACGGGTT
 27801 GACTACTCAA CCCGAATAAA CTACATGAGC GCGGGACCCC ACATGATATC
 CTGATGAGTT GGGCTTATTT GATGTACTCG CGCCCTGGGG TGTACTATAG
 27851 CCGGGTCAAC GGAATACGCG CCCACCGAAA CCGAATTCTC CTGGAACAGG
 GGCCAGTTG CCTTATGCGC GGGTGGCTTT GGCTTAAGAG GACCTTGTC
 27901 CGGCTATTAC CACCACACCT CGTAATAACC TTAATCCCCG TAGTTGGCCC
 CCCGATAATG GTGGTGTGGA GCATTATTGG AATTAGGGGC ATCAACCGGG
 27951 GCTGCCCTGG TGTACCAGGA AAGTCCCGCT CCCACCACTG TGGTACTTCC
 CGACGGGACC ACATGGTCCT TTCAGGGCGA GGGTGGTGAC ACCATGAAGG
 28001 CAGAGACGCC CAGGCCGAAG TTCAGATGAC TAACTCAGGG GCGCAGCTTG
 GTCTCTGCCG GTCCGGCTTC AAGTCTACTG ATTGAGTCCC CGCGTCGAAC
 28051 CGGGCGGCTT TCGTCACAGG GTGCGGTGCG CCGGGCAGGG TATAACTCAC
 GCCCGCCGAA AGCAGTGTC CACGCCAGCG GGCCCGTCCC ATATTGAGTG
 28101 CTGACAATCA GAGGGCGAGG TATTCAGTCT AACGACGAGT CGGTGAGCTC
 GACTGTTAGT CTCCCGCTCC ATAAGTCGAG TTGCTGCTCA GCCACTCGAG
 28151 CTCGCTTGGT CTCCGTCCGG ACGGGACATT TCAGATCGGC GCGCCCGGCC
 GAGCGAACCA GAGGCAGGCC TGCCCTGTAA AGTCTAGCCG CCGCGGCCGG
 28201 GCTCTTCATT CACGCCTCGT CAGGCAATCC TAACTCTGCA GACCTCGTCC
 CGAGAAGTAA GTGCGGAGCA GTCCGTTAGG ATTGAGACGT CTGGAGCAGG
 28251 TCTGAGCCGC GCTCTGGAGG CATTGGAACCT CTGCAATTTA TTGAGGAGTT
 AGACTCGGCG CGAGACCTCC GTAACCTTGA GACGTAAAT AACTCCTCAA
 28301 TGTGCCATCG GTCTACTTTA ACCCCTTCTC GGGACCTCCC GGCCACTATC
 ACACGGTAGC CAGATGAAAT TGGGGAAGAG CCCTGGAGGG CCGGTGATAG
 28351 CGGATCAATT TATTCCTAAC TTTGACGCGG TAAAGGACTC GCGGACGGC
 GCCTAGTTAA ATAAGGATTG AACTGCGCC ATTCTCTGAG CCGCCTGCCG
 28401 TACGACTGAA TGTTAAGTGG AGAGGCAGAG CAACTGCGCC TGAAACACCT
 ATGCTGACTT ACAATTACCC TCTCCGTCTC GTTGACGCGG ACTTTGTGGA

Figure 26 AD

28451 GGTCCACTGT CCGCCGACACA AGTGCTTTGC CCGCGACTCC GGTGAGTTT
CCAGGTGACA GCGGCGGTGT TCACGAAACG GGCCTGAGG CCACTCAAAA

28501 GCTACTTTGA ATTGCCCCGAG GATCATATCG AGGGCCCCGC GCACGGCGTC
CGATGAAACT TAACGGGCTC CTAGTATAGC TCCCGGGCCG CGTGCCGCAG

28551 CGGCTTACCG CCCAGGGAGA GCTTGCCCGT AGCCTGATTC GGGAGTTTAC
GCCGAATGGC GGGTCCCTCT CGAACGGGCA TCGGACTAAG CCCTCAAATG

28601 CCAGCGCCCC CTGCTAGTTG AGCGGGACAG GGGACCCTGT GTTCTCACTG
GGTCGCGGGG GACGATCAAC TCGCCCTGTC CCCTGGGACA CAAGAGTGAC

28651 TGATTTGCAA CTGTCCTAAC CCTGGATTAC ATCAAGATCT TTGTGCCAT
ACTAAACGTT GACAGGATTG GGACCTAATG TAGTTCTAGA AACAACGGTA

28701 CTCTGTGCTG AGTATAATAA ATACAGAAAT TAAATATAC TGGGGCTCCT
GAGACACGAC TCATATTATT TATGTCTTTA ATTTTATATG ACCCCGAGGA

28751 ATCGCCATCC TGTAAACGCC ACCGTCTTCA CCCGCCCAAG CAAACCAAGG
TAGCGGTAGG ACATTTGCGG TGGCAGAAGT GGGCGGGTTC GTTTGGTTCC

28801 CGAACCTTAC CTGGTACTTT TAACATCTCT CCCTCTGTGA TTTACAACAG
GCTTGGAATG GACCATGAAA ATTGTAGAGA GGGAGACACT AAATGTTGTC

28851 TTTCAACCCA GACGGAGTGA GTCTACGAGA GAACCTCTCC GAGCTCAGCT
AAAGTTGGGT CTGCCTCACT CAGATGCTCT CTTGGAGAGG CTCGAGTCGA

28901 ACTCCATCAG AAAAAACACC ACCCTCCTTA CCTGCCGGGA ACGTACGAGT
TGAGGTAGTC TTTTGTGTGG TGGGAGGAAT GGACGGCCCT TGCATGCTCA

28951 GCGTCACCGG CCGCTGCACC ACACCTACCG CCTGACCGTA AACCAGACTT
CGCAGTGGCC GCGGACGTGG TGTGGATGGC GGACTGGCAT TTGGTCTGAA

29001 TTTCCGGACA GACCTCAATA ACTCTGTTTA CCAGAACAGG AGGTGAGCTT
AAAGGCCTGT CTGGAGTTAT TGAGACAAAT GGTCTGTGCC TCCACTCGAA

29051 AGAAAACCTT TAGGGTATTA GGCCAAAGGC GCAGCTACTG TGGGGTTTAT
TCTTTTGGGA ATCCATAAT CCGGTTTCCG CGTCGATGAC ACCCCAAATA

29101 GAACAATTCA AGCAACTCTA CGGGCTATTC TAATTCAGGT TTCTCTAGAA
CTTGTTAAGT TCGTTGAGAT GCGCGATAAG ATTAAGTCCA AAGAGATCTT

29151 TCGGGGTGGG GGTATTCTC TGTCTTGTA TTCTCTTTAT TCTTATACTA
AGCCCCAACC CCAATAAGAG ACAGAACT AAGAGAAATA AGAATATGAT

29201 ACGCTTCTCT GCCTAAGGCT CGCCGCTGTC TGTGTGCACA TTTGCATTTA
TGCGAAGAGA CGGATTCCGA GCGGCGGACG ACACACGTGT AAACGTAAAT

29251 TTGTCAGCTT TTAAACGCT GGGGTCGCCA CCAAGATGA TTAGGTACAT
AACAGTCGAA AAATTTGCGA CCCCAGCGGT GGGTTCTACT AATCCATGTA

29301 AATCCTAGGT TTAATCACC TTGCGTCAGC CCACGGTACC ACCCAAAGG
TTAGGATCCA AATGAGTGGG AACGCAGTCG GGTGCCATGG TGGGTTTTC

29351 TGGATTTTAA GGAGCCAGCC TGTAATGTTA CATTCGCAGC TGAAGCTAAT
ACCTAAAATT CTCGGTCGG ACATTACAAT GTAAGCGTCG ACTTCGATTA

Figure 26 AE

29401 GAGTGCACCA CTTATAAA ATGCACCACA GAACATGAAA AGCTGCTTT
 CTCACGTGGT GAGAATATTT TACGTGGTGT CTTGTACTTT TCGACGAATA
 29451 TCGCCACAAA AACAAAATTG GCAAGTATGC TGTTTATGCT ATTTGGCAGC
 AGCGGTGTTT TTGTTTAAAC CGTTCATACG ACAAATACGA TAAACCGTCG
 29501 CAGGTGACAC TACAGAGTAT AATGTTACAG TTTTCCAGGG TAAAAGTCAT
 GTCCACTGTG ATGTCTCATA TTACAATGTC AAAAGGTCCC ATTTTCAGTA
 29551 AAAACTTTTA TGTATACTTT TCCATTTTAT GAAATGTGCG ACATTACCAT
 TTTTGAAAAT ACATATGAAA AGGTAAAATA CTTTACACGC TGTAAATGTA
 29601 GTACATGAGC AAACAGTATA AGTTGTGGCC CCCACAAAAT TGTGTGGAAA
 CATGTACTCG TTTGTCATAT TCAACACCGG GGGTGTTTTA ACACACCTTT
 29651 ACACTGGCAC TTTCTGCTGC ACTGCTATGC TAATTACAGT GCTCGCTTTG
 TGTGACCGTG AAAGACGACG TGACGATACG ATTAATGTCA CGAGCGAAAC
 29701 GTCTGTACCC TACTCTATAT TAAATACAAA AGCAGACGCA GCTTTATTGA
 CAGACATGGG ATGAGATATA ATTTATGTTT TCGTCTGCGT CGAAATAACT
 29751 GGAAAAGAAA ATGCCTTAAT TTAATAAGTT ACAAAGCTAA TGTCAACCACT
 CCTTTCTTTT TACGGAATTA AATGATTCAA TGTTCGATT ACAGTGGTGA
 29801 AACTGCTTTA CTCGCTGCTT GCAAAACAAA TTCAAAAGT TAGCATTATA
 TTGACGAAAT GAGCGACGAA CGTTTGTGTT AAGTTTTC AATCGTAATAT
 29851 ATTAGAATAG GATTTAAACC CCCCAGTCAT TTCCTGCTCA ATACCATTCC
 TAATCTTATC CTAAATTTGG GGGGCCAGTA AAGGACGAGT TATGGTAAGG
 29901 CCTGAACAAT TGAATCTATG TGGGATATGC TCCAGCGCTA CAACCTTGAA
 GGACTTGTTA ACTGAGATAC ACCCTATACG AGGTCGCGAT GTTGGAACCT
 29951 GTCAGGCTTC CTGGATGTCA GCATCTGACT TTGGCCAGCA CCTGTCCCGC
 CAGTCCGAAG GACCTACAGT CGTAGACTGA AACCGGTCGT GGACAGGGCG
 30001 GGATTGTGTC CAGTCCAACT ACAGCGACCC ACCCTAACAG AGATGACCAA
 CCTAAACAAG GTCAGGTGTA TGTGCTGGG TGGGATTGTC TCTACTGGTT
 30051 CACAACCAAC GCGGCCGCGC CTACCGGACT TACATCTACC ACAAATACAC
 GTGTTGGTTG CGCCGCGCGC GATGGCCTGA ATGTAGATGG TGTTTATGTG
 30101 CCCAAGTTTC TGCTTTGTC AATAACTGGG ATAACCTGGG CATGTGGTGG
 GGGTTCAAAG ACGGAACAG TTATTGACCC TATTGAACCC GTACACCACC
 30151 TTCTCCATAG CGCTTATGTT TGTATGCCTT ATTATTATGT GGCTCATCTG
 AAGAGGTATC GCGAATACAA ACATACGAA TAATAATACA CCGAGTAGAC
 30201 CTGCCTAAAG CGCAAACGCG CCCGACCACC CATCTATAGT CCCATCATTG
 GACGGATTTC GCGTTTGCGC GGGCTGGTGG GTAGATATCA GGGTAGTAAC
 30251 TGCTACACCC AAACAATGAT GGAATCCATA GATTGGACGG ACTGAAACAC
 ACGATGTGGG TTTGTTACTA CCTTAGGTAT CTAACCTGCC TGACTTTGTG
 30301 ATGTTCTTTT CTCTTACAGT ATGATTAAAT GAGACATGAT TCCTCGAGTT
 TACAAGAAAA GAGAATGTCA TACTAATTTA CTCTGTACTA AGGAGCTCAA

Figure 26 AF

30351 TTTATATTAC T CCTTGT TGCCTTTTT TGTGCGTGCT CCAAT C
AAATATAATG ACTGGGAACA ACGCGAAAA ACACGCACGA GGTGTAACCG

30401 TGCGGTTTTCT CACATCGAAG TAGACTGCAT TCCAGCCTTC ACAGTCTATT
ACGCCAAAGA GTGTAGCTTC ATCTGACGTA AGGTCGGAAG TGTGAGATAA

30451 TGCTTTACGG ATTTGTCACC CTCACGCTCA TCTGCAGCCT CATCACTGTG
ACGAAATGCC TAAACAGTGG GAGTCCGAGT AGACGTCGGA GTAGTGACAC

30501 GTCATCGCCT TTATCCAGTG CATTGACTGG GTCTGTGTGC GCTTTGCATA
CAGTAGCGGA AATAGGTCAC GTAACGTACC CAGACACACG CGAAACGTAT

30551 TCTCAGACAC CATCCCCAGT ACAGGGACAG GACTATAGCT GAGCTTCTTA
AGAGTCTGTG GTAGGGGTCA TGTCCCTGTC CTGATATCGA CTCGAAGAAT

30601 GAATTCTTTA ATTATGAAAT TTACTGTGAC TTTTCTGCTG ATTATTTGCA
CTTAAGAAAT TAATACTTTA AATGACACTG AAAAGACGAC TAATAAACGT

30651 CCCTATCTGC GTTTTGTTC CCGACCTCCA AGCCTCAAAG ACATATATCA
GGGATAGACG CAAAACAAGG GGCTGGAGGT TCGGAGTTTC TGTATATAGT

30701 TGCAGATTCA CTCGTATATG GAATATTCCA AGTTGCTACA ATGAAAAAAG
ACGTCTAAGT GAGCATATAC CTTATAAGGT TCAACGATGT TACTTTTTTC

30751 CGATCTTTCC GAAGCCTGGT TATATGCAAT CATCTCTGTT ATGGTGTCTT
GCTAGAAAGG CTTGCGACCA ATATACGTTA GTAGAGACAA TACCACAAGA

30801 GCAGTACCAT CTTAGCCCTA GCTATATATC CCTACCTTGA CATTTGGCTGG
CGTCATGGTA GAATCGGGAT CGATATATAG GGATGGAAC GTAAACCGACC

30851 AACGCAATAG ATGCCATGAA CCACCCAACT TTCCCCGCGC CCGCTATGCT
TTGCGTTATC TACGGTACTT GGTGGGTGTA AAGGGGCGCG GCGGATACGA

30901 TCCACTGCAA CAAGTTGTTG CCGGCGGCTT TGTCCCAGCC AATCAGCCTC
AGGTGACGTT GTTCAACAAC GGCCGCCGAA ACAGGGTCGG TTAGTCGGAG

30951 GCCCACCTTC TCCCACCCCT ACTGAAATCA GCTACTTTAA TCTAACAGGA
CGGTGGAAG AGGGTGGGGG TGACTTTAGT CGATGAAATT AGATTGTCCT

31001 GGAGATGACT GACACCCTAG ATCTAGAAAT GGACGGAATT ATTACAGAGC
CCTCTACTGA CTGTGGGATC TAGATCTTTA CCTGCCTTAA TAATGTC TCG

31051 AGCGCCTGCT AGAAAGACGC AGGGCAGCGG CCGAGCAACA GCGCATGAAT
TCGCGGACGA TCTTCTGCG TCCGTCGCC GGCTCGTTGT CCGGTACTTA

31101 CAAGAGCTCC AAGACATGGT TAACTTGAC CAGTGCAAAA GGGGTATCTT
GTCTCGAGG TTCTGTACCA ATTGAACGTG GTCACGTTTT CCCCATAGAA

31151 TTGTCTCGTA AAGCAGGCCA AAGTCACCTA CGACAGTAAT ACCACCGGAC
AACAGAGCAT TTCGTCCGGT TTCAGTGGAT GCTGTCAATTA TGGTGGCCTG

31201 ACCGCCTTAG CTACAAGTTG CCAACCAAGC GTCAGAAATT GGTGGTCATG
TGGCGGAATC GATGTTCAAC GGTGGTTTCG CAGTCTTTAA CCACCACTAC

31251 GTGGGAGAAA AGCCCATAC CATAACTCAG CACTCGGTAG AAACCGAAGG
CACCTCTTT TCGGGTAATG GTATTGAGTC GTGAGCCATC TTTGGCTTCC

Figure 26 A6

31301 CTGCATTACAC TCTTGTGTC AAGGACCTGA GGATCTCTGC ACCCTTCTA
 GACGTAAGTG AGTGGAAACAG TTCCTGGACT CCTAGAGACG TGGGAATATAT

31351 AGACCCTGTG CGGTCTCAAA GATCTTATTC CCTTTAACTA ATAAAAAAAA
 TCTGGGACAC GCCAGAGTTT CTAGAATAAG GGAAATTGAT TATTTTTTTT

31401 ATAATAAAGC ATCACTTACT TAAATCAGT TAGCAAATTT CTGTCCAGTT
 TATTATTTCG TAGTGAATGA ATTTTAGTCA ATCGTTTAAA GACAGGTCAA

31451 TATTCAGCAG CACCTCCTTG CCCTCCTCCC AGCTCTGGTA TTGCAGCTTC
 ATAAGTCGTC GTGGAGGAAC GGGAGGAGGG TCGAGACCAT AACGTCGAAG

31501 CTCCTGGCTG CAAACTTCTT CCACAATCTA AATGGAATGT CAGTTTCCTC
 GAGGACCGAC GTTGAAAGA GGTGTTAGAT TTACCTTACA GTCAAAGGAG

31551 CTGTTCTGTG CCATCCGCAC CCACTATCTT CATGTTGTTG CAGATGAAGC
 GACAAGGACA GGTAGGCGTG GGTGATAGAA GTACAACAAC GTCTACTTCG

31601 GCGCAAGACC GTCTGAAGAT ACCTTCAACC CCGTGTATCC ATATGACACG
 CGCGTTCTGG CAGACTTCTA TGGAAGTTGG GGCACATAGG TATACTGTGC

31651 GAAACCGGTC CTCCAACGTG GCCTTTTCTT ACTCCTCCCT TTGTATCCCC
 CTTTGGCCAG GAGGTTGACA CGGAAAAGAA TGAGGAGGGA AACATAGGGG

31701 CAATGGGTTT CAAGAGAGTC CCCCTGGGGT ACTCTCTTTG CGCCTATCCG
 GTTACCCAAA GTTCTCTCAG GGGGACCCCA TGAGAGAAAC GCGGATAGGC

31751 AACCTCTAGT TACCTCCAAT GGCATGCTTG CGCTCAAAAT GGGCAACGGC
 TTGGAGATCA ATGGAGGTTA CCGTACGAAC GCGAGTTTAA CCCGTTGCCG

31801 CTCTCTCTGG ACGAGGCCCG CAACCTTACC TCCCAAAATG TAACCACTGT
 GAGAGAGACC TGCTCCGGCC GTTGAATGG AGGGTTTAC ATTGGTGACA

31851 GAGCCACCT CTCAAAAAA CCAAGTCAAA CATAAACCTG GAAATATCTG
 CTCGGGTGGA GAGTTTTTTT GGTTCAGTTT GTATTTGGAC CTTTATAGAC

31901 CACCCCTCAC AGTTACCTCA GAAGCCCTAA CTGTGGCTGC CGCCGCACCT
 GTGGGGAGTG TCAATGGAGT CTTCGGGATT GACACCGACG GCGGCGTGGA

31951 CTAATGGTCG CGGGCAACAC ACTCACCATG CAATCACAGG CCCCGCTAAC
 GATTACCAGC GCCCGTTGTG TGAGTGGTAC GTTAGTGTC GGGGCGATTG

32001 CGTGCACGAC TCCAAACTTA GCATTGCCAC CCAAGGACCC CTCACAGTGT
 GCACGTGCTG AGGTTTGAAT CGTAACGGTG GGTTCCTGGG GAGTGTGACA

32051 CAGAAGGAAA GCTAGCCCTG CAAACATCAG GCCCCCTCAC CACCACCGAT
 GTCTTCCTTT CGATCGGGAC GTTGTAGTC CGGGGGAGTG GTGGTGGCTA

32101 AGCAGTACCC TTACTATCAC TGCCTCACCC CCTCTAACTA CTGCCACTGG
 TCGTCATGGG AATGATAGTG ACGGAGTGGG GGAGATTGAT GACGGTGACC

32151 TAGCTTGGGC ATTGACTTGA AAGAGCCCAT TTATACACAA AATGGAAAAC
 ATCGAACCCG TAACTGAACT TTCTCGGGA AATATGTGTT TTACCTTTTG

32201 TAGGACTAAA GTACGGGGCT CCTTTGCATG TAACAGACGA CCTAAACACT
 ATCCTGATTT CATGCCCGA GGAAACGTAC ATTGTCTGCT GGATTGTGA

Figure 26 AH

32251 TTGACCGTAG CTGGTCC AGGTGTGACT ATTAATAATA CTTCCTTCA
AACTGGCATC GACACAGG TCCACACTGA TAATTATTAT GAAGGAGT

32301 AACTAAAGTT ACTGGAGCCT TGGGTTTTGA TTCACAAGGC AATATGCAAC
TTGATTTCAA TGACCTCGGA ACCCAAACCT AAGTGTTCG TTATACGTTG

32351 TTAATGTAGC AGGAGGACTA AGGATTGATT CTCAAAACAG ACGCCTTATA
AATTACATCG TCCTCCTGAT TCCTAACTAA GAGTTTTGTC TCGGGAATAT

32401 CTTGATGTTA GTTATCCGTT TGATGCTCAA AACCAACTAA ATCTAAGACT
GAACTACAAT CAATAGGCAA ACTACGAGTT TTGGTTGATT TAGATTCTGA

32451 AGGACAGGGC CCTCTTTTTA TAAACTCAGC CCACAACCTG GATATTAACCT
TCCTGTCCCG GGAGAAAAAT ATTTGAGTCG GGTGTGAAC CTATAATTGA

32501 ACAACAAAGG CCTTTACTTG TTTACAGCTT CAAACAATTC CAAAAAGCTT
TGTGTTTTCC GGAAATGAAC AAATGTCGAA GTTTGTTAAG GTTTTTCGAA

32551 GAGGTTAACC TAAGCACTGC CAAGGGGTTG ATGTTTGACG CTACAGCCAT
CTCCAATTGG ATTCGTGACG GTTCCCAAC TACAACTGC GATGTCGGTA

32601 AGCCATTAAT GCAGGAGATG GGCTTGAATT TGGTTCACCT AATGCACCAA
TCGGTAATTA CGTCCTCTAC CCGAACTTAA ACCAAGTGA TTACGTGGTT

32651 ACACAAATCC CCTCAAAACA AAAATTGGCC ATGGCCTAGA ATTTGATTCA
TGTGTTTAGG GGAGTTTGT TTTTAACCG TACCGATCT TAACTAAGT

32701 AACAAAGCTA TGGTTCCTAA ACTAGGAAC GGCCTTAGTT TTGACAGCAC
TTGTTCCGAT ACCAAGGATT TGATCCTGA CCGGAATCAA AACTGTCGTG

32751 AGGTGCCATT ACAGTAGGAA ACAAAAATAA TGATAAGCTA ACTTTGTGGA
TCCACGGTAA TGTCATCCTT TGTTTTTATT ACTATTCGAT TGAAACACCT

32801 CCACACCAGC TCCATCTCCT AACTGTAGAC TAAATGCAGA GAAAGATGCT
GGTGTGGTCG AGGTAGAGGA TTGACATCTG ATTTACGTCT CTTTCTACGA

32851 AAACCTCACTT TGGTCTTAAC AAAATGTGGC AGTCAAATAC TTGCTACAGT
TTTGAGTGAA ACCAGAAATTG TTTTACACCG TCAGTTTATG AACGATGTCA

32901 TTCAGTTTG GCTGTTAAAG GCAGTTTGGC TCCAATATCT GGAACAGTTC
AAGTCAAAC CGACAATTTC CGTCAAACCG AGGTTATAGA CCTTGTCAG

32951 AAAGTGCTCA TCTTATTATA AGATTTGACG AAAATGGAGT GCTACTAAAC
TTTCACGAGT AGAATAATAT TCTAACTGC TTTTACCTCA CGATGATTTG

33001 AATTCCTTCC TGGACCCAGA ATATTGGAAC TTTAGAAATG GAGATCTTAC
TTAAGGAAGG ACCTGGGTCT TATAACCTTG AAATCTTTAC CTCTAGAATG

33051 TGAAGGCACA GCCTATACAA ACGCTGTTGG ATTTATGCCT AACCTATCAG
ACTTCCGTGT CGGATATGTT TCGGACAACC TAAATACGGA TTGGATAGTC

33101 CTTATCCAAA ATCTCACGGT AAAACTGCCA AAAGTAACAT TGTCAGTCAA
GAATAGGTTT TAGAGTGCCA TTTTGACGGT TTTTATTGTA ACAGTCAGTT

33151 GTTACTTAA ACGGAGACAA AACTAAACCT GTAACACTAA CCATTACACT
CAAATGAATT TGCCTCTGTT TTGATTTGGA CATGTGATT GGTAAATGTA

Figure 26 AI

33201 AAACGGTACA C GAAACAG GAGACACAAC TCCAAGTGCA TACTCTTCT
 TTTGCCATGT GTCTTTGTC CTCTGTGTTG AGGTTACCGT ATGAGATACA
 33251 CATTTTCATG GGACTGGTCT GGCCACAAC ACATTAAATGA AATATTTGCC
 GTAAAAGTAC CCGTACCAGA CCGGTGTTGA TGTAAATTA TTTATAAACGG
 33301 ACATCCTCTT ACACTTTTTC ATACATTGCC CAAGAATAAA GAATCGTTTG
 TGTAGGAGAA TGTGAAAAAG TATGTAACGG GTTCTTATTT CTTAGCAAAC
 33351 TGTATGTTT CAACGTGTTT ATTTTCAAT TGCAGAAAAT TTCAAGTCAT
 ACAATACAAA GTTGACAAA TAAAAAGTTA ACGTCTTTTA AAGTTAGTA
 33401 TTTTCATTCA GTAGTATAGC CCCACCACCA CATAGCTTAT ACAGATCACC
 AAAAGTAAGT CATCATATCG GGGTGGTGGT GTATCGAATA TGTCTAGTGG
 33451 GTACCTTAAT CAACTCACA GAACCTAGT ATTCAACCTG CCACCTCCCT
 CATGGAATTA GTTTGAGTGT CTTGGGATCA TAAGTTGGAC GGTGGAGGGA
 33501 CCCAACACAC AGAGTACACA GTCCTTTCTC CCCGGCTGGC CTTAAAAAGC
 GGGTTGTGTG TCTCATGTGT CAGGAAAGAG GGGCCGACCG GAATTTTTCG
 33551 ATCATATCAT GGGTAACAGA CATATTCTTA GTGTTATAT TCCACACGGT
 TAGTATAGTA CCCATTGTCT GTATAAGAAT CCACAATATA AGGTGTGCCA
 33601 TTCCTGTCGA GCCAAACGCT CATCAGTGAT ATTAATAAAC TCCCCGGGCA
 AAGGACAGCT CGGTTTGC GAAGTCACTA TAATTATTG AGGGGCCCGT
 33651 GCTCACTTAA GTTCATGTCG CTGTCCAGCT GCTGAGCCAC AGGCTGCTGT
 CGAGTGAATT CAAGTACAGC GACAGGTGGA CGACTCGGTG TCCGACGACA
 33701 CCAACTTGCG GTTGCTTAAC GGGCGGCGAA GGAGAAGTCC ACGCCTACAT
 GGTGAACGC CAACGAATTG CCCGCCGCTT CTCTTCAGG TCGGGATGTA
 33751 GGGGGTAGAG TCATAATCGT GCATCAGGAT AGGGCGGTGG TGCTGCAGCA
 CCCCCATCTC AGTATTAGCA CGTAGTCTTA TCCCGCCACC ACGACGTCGT
 33801 GCGCGCGAAT AAATGCTGC CGCCGCCGCT CCGTCTGCA GGAATACAAC
 CGCGCGCTTA TTTGACGACG GCGCGGCGGA GGCAGGACGT CTTATGTTG
 33851 ATGGCAGTGG TCTCCTCAGC GATGATTCGC ACCGCCCCGA GCATAAGGCG
 TACCGTCACC AGAGGAGTCG CTACTAAGCG TGGCGGGCGT CGTATTCCGC
 33901 CCTGTCTCTC CGGGCACAGC AGCGCACCCCT GATCTCACTT AAATCAGCAC
 GGAACAGGAG GCCCGTGTG TCGCGTGGGA CTAGAGTGAA TTTAGTCGTG
 33951 AGTAACTGCA GCACAGCACC ACAATATTGT TCAAAATCCC ACAGTGCAAG
 TCATTGACGT CGTGTGCTGG TGTATAACA AGTTTATAGG TGTACGTTT
 34001 GCGCTGTATC CAAAGCTCAT GCGGGGGACC ACAGAACCCA CGTGGCCATC
 CGCGACATAG GTTTCGAGTA CCGCCCCGTT TGTCTTGGGT GCACCGGTAG
 34051 ATACCACAAG CGCAGGTAGA TTAAGTGGCG ACCCCTCATA AACACGCTGG
 TATGGTGTTC GCGTCCATCT AATCACCOC TGGGGAGTAT TTGTGCGACC
 34101 ACATAAACAT TACCTCTTTT GGCATGTTGT AATCACCAC CTCCCGGTAC
 TGTATTTGTA ATGGAGAAAA CCGTACAACA TTAAGTGGTG GAGGGCCATG

Figure 26 AJ

34151 CATATAAACC TATTAATAA CATGGCGCCA TCCACCACCA TCCTATTA
GTATATTGG ATCTAATTT GTACCGCGGT AGGTGGTGGT AGGATTGGT

34201 GCTGGCCAAA ACCTGCCCGC CGGCTATACA CTGCAGGGAA CCGGACTGG
CGACCGGTTT TGGACGGGCG GCCGATATGT GACGTCCCTT GGCCCTGACC

34251 AACAAATGACA GTGGAGAGCC CAGGACTCGT AACCATGGAT CATCATGCTC
TTGTTACTGT CACCTCTCGG GTCCTGAGCA TTGGTACCTA GTAGTACGAG

34301 GTCATGATAT CAATGTTGGC ACAACACAGG CACACGTGCA TACACTTCCT
CAGTACTATA GTTACAACCG TGTGTGTCC GTGTGCACGT ATGTGAAGGA

34351 CAGGATTACA AGCTCCTCCC GCGTTAGAAC CATATCCCAG GGAACAACCC
GTCCTAATGT TCGAGGAGGG CGCAATCTTG GTATAGGGTC CCTGTTGGG

34401 ATTCTGAAT CAGCGTAAAT CCCACACTGC AGGGAAGACC TCGCACGTAA
TAAGGACTTA GTCGCATTTA GGGTGTGACG TCCCTTCTGG AGCGTGCATT

34451 CTCACGTTGT GCATTGTCAA AGTGTACAT TCGGGCAGCA GCGGATGATC
GAGTGCAACA CGTAACAGTT TCACAATGTA AGCCCGTCGT CGCCTACTAG

34501 CTCCAGTATG GTAGCGCGGG TTTCTGTCTC AAAAGGAGGT AGACGATCCC
GAGGTCATAC CATCGCGCCC AAAGACAGAG TTTTCTCCA TCTGCTAGGG

34551 TACTGTACGG AGTGCGCCGA GACAACCGAG ATCGTGTGG TCGTAGTGTG
ATGACATGCC TCACGCGGCT CTGTTGGCTC TAGCACAACC AGCATCACAG

34601 ATGCCAAATG GAACGCCGGA CGTAGTCATA TTTCTGAAG CAAAACCAGG
TACGGTTTAC CTTGCGGCTT GCATCAGTAT AAAGGACTTC GTTTTGGTCC

34651 TCGGGGCGTG ACAAACAGAT CTGCGTCTCC GGTCTCGCCG CTTAGATCGC
ACGCCCCGAC TGTGTGTCTA GACGAGAGG CCAGAGCGGC GAATCTAGCG

34701 TCTGTGTAGT AGTTGTAGTA TATCCACTCT CTCAAAGCAT CCAGGCGCCC
AGACACATCA TCAACATCAT ATAGGTGAGA GAGTTTCGTA GGTCCGCGGG

34751 CCTGGGCTCG GGTTCATGT AACTCCTTC ATGCGCGCT GCCCTGATAA
GGACCGAAGC CCAAGATACA TTTGAGGAAG TACGCGCGCA CGGGACTATT

34801 CATCCACCAC CGCAGAATAA GCCACACCCA GCCAACCTAC ACATTGTTT
GTAGGTGGTG GCGTCTTATT CCGTGTGGGT CCGTTGGATG TGTAAGCAAG

34851 TCGGAGTCAC ACACGGGAGG AGCGGGAAGA GCTGGAAGAA CCATGTTTTT
ACGCTCAGTG TGTGCCCTCC TCGCCCTTCT CGACCTTCTT GGTACAAAAA

34901 TTTTTTATTC CAAAAGATTA TCCAAAACCT CAAAATGAAG ATCTATTAAG
AAAAAATAAG GTTTTCTAAT AGGTTTGGGA GTTTTACTTC TAGATAATTC

34951 TGAACGCGCT CCCCTCCGGT GCGGTGSTCA AACTCTACAG CCAAAGAACA
ACTTGCGCGA GGGGAGGCCA CCGCACCAGT TTGAGATGTC GGTTCCTTGT

35001 GATAATGGCA TTTGTAAGAT GTTGACAAT GGCTTCCAA AGGCAAACGG
CTATTACCGT AAACATTCTA CAACGTGTTA CCGAAGGTTT TCCGTTTGCC

35051 CCCTCACGTC CAAGTGGACG TAAAGGCTAA ACCCTTCAGG GTGAATCTCC
GGGAGTGACG GTTACCTGC ATTTCCGATT TGGGAAGTCC CACTTAGAGG

Figure 26 AK

35101 TCTATAAACA TTAGCACC TTCAACCATG CCCAAATAAT TCTCAT G
AGATATTTGT AAGGTCGTGG AAGTTGGTAC GGTTTATTA AGAGTAGGC

35151 CCACCTTCTC AATATATCTC TAAGCAAATC CCGAATATTA AGTCCGGCCA
GGTGAAGAG TTATATAGAG ATTCGTTTAG GGCTTATAAT TCAGGCCGGT

35201 TTGTAAAAAT CTGCTCCAGA GCGCCCTCCA CCTTCAGCCT CAAGCAGCGA
AACATTTTGA GACGAGGTCT CGCGGGAGGT GGAAGTCGGA GTTCGTCGCT

35251 ATCATGATTG CAAAAATTCA GGTTCCTCAC AGACCTGTAT AAGATTCAAA
TAGTACTAAC GTTTTAAAGT CCAAGGAGTG TCTGGACATA TTCTAAGTTT

35301 AGCGGAACAT TAACAAAAAT ACCGCGATCC CGTAGGTCCC TTCGCAGGGC
TCGCCCTGTA ATTGTTTMTA TGGCGCTAGG GCATCCAGGG AAGCGTCCCG

35351 CAGCTGAACA TAATCGTGCA GGTCTGCACG GACCAGCGCG GCCACTTCCC
GTCGACTTGT ATTAGCACGT CCAGACGTGC CTGGTCGCGC CGGTGAAGGG

35401 CGCCAGGAAC CATGACAAAA GAACCCACAC TGATTATGAC ACGCATACTC
GCGGTCCTTG GTACTGTTTT CTGGGGTGTG ACTAATACTG TCGGTATGAG

35451 GGAGCTATGC TAACCAGCGT AGCCCCGATG TAAGCTTGTT GCATGGGCGG
CCTCGATACG ATTGGTCGCA TCGGGGCTAC ATTGGAACAA CGTACCCGCC

35501 CGATATAAAA TGCAAGGTGC TGCTCAAAAA ATCAGGCAAA GCCTCGCGCA
GCTATATTTT ACGTTCACG ACGAGTTTTT TAGTCCGTTT CGGAGCGCGT

35551 AAAAAGAAAG CACATCGTAG TCATGCTCAT GCAGATAAG GCAGGTAAGC
TTTTTCTTTC GTGTAGCATC AGTACGAGTA CGTCTATTTT CGTCCATTCTG

35601 TCCGGAACCA CCACAGAAAA AGACACCATT TTTCTCTCAA ACATGTCTGC
AGGCCCTGGT GGTGCTTTTT TCTGTGGTAA AAAGAGAGTT TGTACAGACG

35651 GGGTTTCTGC ATAAACACAA AATAAAATAA CAAAAAACA TTAAACATT
CCCAAAGACG TATTTGTGTT TTATTTTATT GTTTTTTTGT AAATTTGTAA

35701 AGAAGCCTGT CTTACAACAG GAAAAACAAC CTTATAAGC ATAAGACGGA
TCTTCGGACA GAATGTTGTC CTTTTTGTG GGAATATTCG TATTCTGCCT

35751 CTACGGCCAT GCCGGCGTGA CCGTAAAAAA ACTGGTCACC GTGATTAAAA
GATGCCGGTA CGGCCGCACT GGCATTTTTT TGACCACTGG CACTAATTTT

35801 AGCACCACCG ACAGCTCCTC GGTGATGTCC GGAGTCATAA TGTAAGACTC
TCGTGGTGGC TGTGAGGAG CCAGTACAGG CCTCAGTATT ACATTCTGAG

35851 GGTAAACACA TCAGGTTGAT TCACATCGGT CAGTGCTAAA AAGCGACCGA
CCATTTGTGT AGTCCAAC TAAGTAGCCA GTCACGATTT TTCGCTGGCT

35901 AATAGCCCGG GGAATACAT ACCCGCAGGC GTAGAGACAA CATTACAGCC
TTATCGGGCC CCCTTATGTA TGGGCGTCCG CATCTCTGTT GTAATGTCGG

35951 CCCATAGGAG GTATAACAAA ATTAATAGGA GAGAAAAACA CATAAACACC
GGGTATCCTC CATATTGTTT TAATTATCCT CTCTTTTGT GTATTGTGG

36001 TGAAAAACCC TCCTGCCTAG GCAAAATAGC ACCCTCCCGC TCCAGAACAA
ACTTTTGGG AGGACGGATC CGTTTATCG TGGGAGGGCG AGGTCTTGTT

Figure 26 AL

36051 CATACAGCGC TACAGCG GCAGCCATAA CAGTCAGCCT TACCAG A
 GTATGTCGCG AAGGTGTCGC CGTCGGTATT GTCAGTCGGA ATGGTCATT
 36101 AAAGAAAACC TATTAAAAA ACACCACTCG ACACGGCACC AGCTCAATCA
 TTCTTTTGG ATAATTTTTT TGTGGTGAGC TGTGCCGTGG TCGAGTTAGT
 36151 GTCACAGTGT AAAAAAGGGC CAAGTGCGA GCGAGTATAT ATAGGACTAA
 CAGTGTCACA TTTTTCCTCCG GTTCACGTCT CGCTCATATA TATCCTGATT
 36201 AAAATGACGT AACGGTTAAA GTCCACAAA AACACCCAGA AAACCGCACG
 TTTTACTGCA TTGCCAATTT CAGGTGTTTT TTGTGGGTCT TTGGCGTGC
 36251 CGAACCTACG CCCAGAAACG AAAGCCAAA AACCCACAAC TTCCTCAAAT
 GCTTGGATGC GGTCTTTTGC TTTCGGTTTT TTGGGTGTTG AAGGAGTTA
 36301 CGTCACTTCC GTTTTCCAC GTTACGTAC TTCCATTTT AAGAAAACCTA
 GCAGTGAAGG CAAAAGGGTG CAATGCAGTG AAGGGTAAAA TTCTTTTGAT
 36351 CAATTCCCAA CACATACAAG TTAATCCGCC CTAAAACCTA CGTACCCCGC
 GTTAAGGGTT GTGTATGTT AATGAGGCGG GATTTTGGAT GCAGTGGGCG
 36401 CCCGTTCCCA CGCCCCGCGC CACGTACAA ACTCCACCCC CTCATTATCA
 GGGCAAGGGT GCGGGGCGCG GTGCAGTGT TGAGGTGGG GAGTAATAGT
 PacI

 36451 TATTGGCTTC AATCCAAAAT AAGGTATATT ATTGATGATG TTAATTAAGA
 ATAACCGAAG TTAGGTTTTA TTCCATATAA TAACTACTAC AATTAATTCT
 36501 ATTCCGATCT GCGACGCGAG GCTGGATGGC CTTCCCCATT ATGATTCTTC
 TAAGCCTAGA CGTGCCTC CGACCTACCG GAAGGGGTAA TACTAAGAAG
 36551 TCGCTTCCGG CGGCATCGGG ATGCCCCGCT TGCAGGCCAT GCTGTCCAGG
 AGCGAAGGCC GCCGTAGCCC TACGGGCGCA ACGTCCGGTA CGACAGGTCC
 36601 CAGGTAGATG ACGACCATCA GGGACAGCTT CAAGGCCAGC AAAAGGCCAG
 GTCCATCTAC TGCTGGTAGT CCCTGTCGAA GTTCCGGTCG TTTTCCGGTC
 36651 GAACCGTAAA AAGGCCGCGT TGCTGGCGTT TTTCCATAGG CTCCGCCCCC
 CTTGGCATT TTCCGGCGCA ACGACCGCAA AAAGGTATCC GAGGCGGGG
 36701 CTGACGAGCA TCACAAAAAT CGACGCTCAA GTCAGAGGTG GCGAAACCG
 GACTGCTCGT AGTGTTTTTA GCTGCGAGT CAGTCTCCAC CGCTTTGGG
 36751 ACAGGACTAT AAAGATACCA GCGTTTCCC CCTGGAAGCT CCCTCGTGCG
 TGTCCTGATA TTTCTATGGT CCGCAAAGGG GGACCTTCGA GGGAGCACGC
 36801 CTCTCCTGTT CCGACCTGCG CGCTTACCGG ATACCTGTCC GCCTTTCTCC
 GAGAGGACAA GGCTGGGACG GCGAATGGCC TATGGACAGG CGGAAAGAGG
 36851 CTTCCGGGAAG CGTGGCGCTT TCTCATAGCT CACGCTGTAG GTATCTCAGT
 GAAGCCCTTC GCACCGCGAA AGAGTATCGA GTGCGACATC CATAGAGTCA
 36901 TCGGTGTAGG TCGTTGCTC CAAGCTGGGC TGTGTGCACG AACCCCGGT
 AGCCACATCC AGCAAGCGAG GTTCGACCG ACACACGTGC TTGGGGGGCA

Figure 26 AM

36951 TCAGCCCGAC GCGGCCT TATCCGGTAA CTATCGTCTT GAGTCG CCG
 AGTCGGGCTG GCGACGCGGA ATAGGCCATT GATAGCAGAA CTCAGGTTGG
 37001 CCGTAAGACA CGACTTATCG CCACTGGCAG CAGCCACTGG TAACAGGATT
 GCCATTCTGT GCTGAATAGC GGTGACCGTC GTCGGTGACC ATTGTCCTAA
 37051 AGCAGAGCGA GGTATGTAGG CCGTGCTACA GAGTTCTTGA AGTGGTGGCC
 TCGTCTCGCT CCATACATCC GCCACGATGT CTCAAGAACT TCACCACCGG
 37101 TAACTACGGC TACACTAGAA GGACAGTATT TGGTATCTGC GCTCTGCTGA
 ATTGATGCCG ATGTGATCTT CCTGTCATAA ACCATAGACG CGAGACGACT
 37151 AGCCAGTTAC CTTCGGAAAA AGAGTTGGTA GCTCTTGATC CGGCAAACAA
 TCGGTCAATG GAAGCCTTTT TCTCAACCAT CGAGAAGTAG GCCGTTTGTT
 37201 ACCACCGCTG GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC AGATTACGCG
 TGGTGGCGAC CATCGCCACC AAAAAACAA ACGTTCGTCG TCTAATGCGC
 37251 CAGAAAAAAA GGATCTCAAG AAGATCCTTT GATCTTTTCT ACGGGGCTCG
 GTCTTTTTTT CCTAGAGTTC TTCTAGGAAA CTAGAAAAGA TGCCCCAGAC
 37301 ACGCTCAGTG GAACGAAAAC TCACGTTAAG GGATTTTGGT CATGAGATTA
 TGCGAGTCAC CTTGCTTTTG AGTGCAATTC CCTAAAACCA GTACTCTAAT
 37351 TCAAAAAGGA TCTTCACCTA GATCCTTTTA AATCAATCTA AAGTATATAT
 AGTTTTTCCT AGAAGTGGAT CTAGGAAAAT TTAGTTAGAT TTCATATATA
 37401 GAGTAAACTT GGTCTGACAG TTACCAATGC TTAATCAGTG AGGCACCTAT
 CTCATTTGAA CCAGACTGTC AATGGTTACG AATTAGTCAC TCCGTGGATA
 37451 CTCAGCGATC TGTCTATTTT GTTCATCCAT AGTTGCCTGA CTCCCCGTCG
 GAGTCGCTAG ACAGATAAAG CAAGTAGGTA TCAACGGACT GAGGGGCAGC
 37501 TGTAAGATAAC TACGATACGG GAGGGCTTAC CATCTGGCCC CAGTGCTGCA
 ACATCTATTG ATGCTATGCC CTCCCGAATG GTAGACCGGG GTCACGACGT
 37551 ATGATACCGC GAGACCCACG CTCACCGGCT CCAGATTTAT CAGCAATAAA
 TACTATGGCG CTCTGGGTGC GAGTGGCCGA GGTCTAAATA GTCGTTATTT
 37601 CCAGCCAGCC GGAAGGGCCG AGCGCAGAAG TGGTCCTGCA ACTTTATCCG
 GGTCCGTCGG CCTTCCCGGC TCGCGTCTTC ACCAGGACGT TGAATAGGC
 37651 CCTCCATCCA GTCTATTAAT TGTGCGCGG AAGCTAGAGT AAGTAGTTCG
 GGAGGTAGGT CAGATAATTA ACAACGGCCC TTCGATCTCA TTCATCAAGC
 37701 CCAGTTAATA GTTTGCGCAA CGTTGTTGCC ATTGCTACAG GCATCGTGGT
 GGTCAATTAT CAAACGCGTT GCAACAACGG TAACGATGTC CGTAGCACC
 37751 GTCACGCTCG TCGTTTGGA TGGCTTCATT CAGCTCCGGT TCCCAACGAT
 CAGTCCGAGC AGCAAACCAT ACCGAAGTAA GTCGAGGCCA AGGTTGCTA
 37801 CAAGGCGAGT TACATGATCC CCCATGTTGT GCAAAAAAGC GGTAGCTCC
 GTTCCGCTCA ATGTACTAGG GGGTACAACA CGTTTTTCG CCAATCGAGG
 37851 TTCGGTCTCT CGATCGTTGT CAGAAAGTAA TTGGCCGAG TGTATCACT
 AAGCCAGGAG GCTAGCAACA GTCTTCATT CACCGCGTC ACAATAGTGA

Figure 26 AN

37901 CATGGTTATG CACTGC ATAATTCTCT TACTGTCATG CCATCGTAA
GTACCAATAC CGTCGTGACG TATTAAGAGA ATGACAGTAC GGTAGGCTTT

37951 GATGCTTTTC TGTGACTGGT GAGTACTCAA CCAAGTCATT CTGAGAATAG
CTACGAAAAG ACACTGACCA CTCATGAGTT GGTTCAGTAA GACTCTTATC

38001 TGTATGCGGC GACCGAGTTG CTCTTGCCCG GCGTCAACAC GGGATAATAC
ACATACGCCG CTGGCTCAAC GAGAACGGGC CGCAGTTGTG CCCTATTATG

38051 CGCGCCACAT AGCAGAACTT TAAAAGTGCT CATCATTGGA AAACGTTCTT
GCGCGGTGTA TCGTCTTGAA ATTTTCACGA GTAGTAACCT TTTGCAAGAA

38101 CGGGGCGAAA ACTCTCAAGG ATCTTACCGC TGTGAGATC CAGTTCGATG
GCCCCGCTTT TGAGAGTTCC TAGAATGGCG ACAACTCTAG GTCAAGCTAC

38151 TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG
ATTGGGTGAG CACGTGGGTT GACTAGAAGT CGTAGAAAAT GAAAGTGSTC

38201 CGTTTCTGGG TGAGCAAAAA CAGGAAGGCA AAATGCCGCA AAAAAGGGAA
GCAAAGACCC ACTCGTTTTT GTCCCTCCGT TTTACGGCGT TTTTCCCTT

38251 TAAGGGCGAC ACGGAAATGT TGAATACTCA TACTCTTCCT TTTTCAATAT
ATTCCCGCTG TGCCTTTACA ACTTATGAGT ATGAGAAGGA AAAAGTTATA

38301 TATTGAAGCA TTTATCAGGG TTATTGTCTC ATGAGCGGAT ACATATTGA
ATAACTTCGT AAATAGTCCC AATAACAGAG TACTCGCCTA TGTATAAACT

38351 ATGTATTTAG AAAAATAAAC AAATAGGGGT TCCGCGCACA TTTCCCCGAA
TACATAAATC TTTTATTG TTTATCCCCA AGGCGCGTGT AAAGGGGCTT

38401 AAGTGCCACC TGACGTCTAA GAAACCATTA TTATCATGAC ATTAACCTAT
TTCACGGTGG ACTGCAGATT CTTTGGTAAT AATAGTACTG TAATTGGATA

38451 AAAAATAGGC GTATCACGAG GCCCTTTCGT CTTCAAGAAT TGGATCCGAA
TTTTTATCCG CATAGTGCTC CGGGAAAGCA GAAGTTCTTA ACCTAGGCTT

PacI

38501 TTCTTAATTT CTTAATTAA (SEQ ID NO:32)
AAGAATTAAA GAATTAATT (SEQ ID NO:33)

Figure 26 A0

MRKAd5nef MER1063
 (MRKAd5 Pre-Adenoviral Vector Containing the G2A,LLA nef Coding Region)

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1  CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG
   GTAGTAGTTA TTATATGGAA TAAACCTAA CTTGCGTTAT ACTATTACTC

51  GGGGTGGAGT TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG
   CCCACCTCA AACACTGCAC CGCGCCCCGC ACCCTTGCCC CGCCCACTGC

101 TAGTAGTGTG GCGGAAGTGT GATGTTGCAA GTGTGGCGGA ACACATGTAA
   ATCATCACAC CGCCTTCACA CTACAACGTT CACACCGCCT TGTGTACATT

151 GCGACGGATG TGGCAAAAGT GACGTTTTTG GTGTGCGCCG GTGTACACAG
   CGCTGCCTAC ACCGTTTTCA CTGCAAAAC CACACGCGGC CACATGTGTC

201 GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG TAAATTGGG
   CTTCACTGTT AAAAGCGCGC CAAAATCCGC CTACAACATC ATTTAAACCC

251 CGTAACCGAG TAAGATTGCG CCATTTTCGC GGGAAACTG AATAAGAGGA
   GCATTGGCTC ATTCTAAACC GGTAAAAGCG CCCTTTTGAC TTATTCTCCT

301 AGTGAAATCT GAATAATTTT GTGTTACTCA TAGCGCGTAA TATTTGTCTA
   TCACTTTAGA CTTATTAAAA CACAATGAGT ATCGCGCATT ATAAACAGAT

351 GGGCCGCGGG GACTTTGACC GTTTACGTGG AGACTCGCCC AGGTGTTTTT
   CCCGGCGCCC CTGAAACTGG CAAATGCACC TCTGAGCGGG TCCACAAAAA

401 CTCAGGTGTT TTCCGCGTTC CGGGTCAAAG TTGGCGTTTT ATTATTATAG
   GAGTCCACAA AAGGCGCAAG GCCCAGTTTC AACCGCAAAA TAATAATATC

451 GCGGCCGCGA TCCATTGCAT ACGTTGTATC CATATCATAA TATGTACATT
   CGCCGGCGCT AGGTAACGTA TGCAACATAG GTATAGTATT ATACATGTAA

501 TATATTGGCT CATGTCCAAC ATTACCGCCA TGTTGACATT GATTATTGAC
   ATATAACCGA GTACAGGTTG TAATGGCGGT ACAACTGTAA CTAATAACTG

551 TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA
   ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT

601 TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG
   ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC

651 CCCAACGACC CCCGCCCAT TACGTCAATA ATGACGTATG TTCCCATAGT
   GGGTTGCTGG GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA

701 AACGCCAATA GGGACTTTCC ATGACGTCA ATGGGTGGAG TATTTACGGT
   TTGCGGTTAT CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

751 AAAGTGGCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTACGCCC
   TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCATGCGGG

801 CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCCAGTA
   GGATAACTGC AGTTACTGCC ATTTACGGG CGGACCGTAA TACGGGTCAT
  
```

Figure 27A

851 CATGACCTTA T GACTTTC CTACTTGGCA GTACATCTAC GTATTGCA
GTACTGGAAT ACCCTGAAAG GATGAACCGT CATGTAGATG CATAATCGT

901 TCGCTATTAC CATGGTGATG CGGTTTGGC AGTACATCAA TGGGCGTGGA
AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

951 TAGCGGTTTG ACTCACGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA
ATCGCCAAAC TGAGTGCCCC TAAAGGTICA GAGGTGGGGT AACTGCAGTT

1001 TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA
ACCCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

1051 ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG
TGTGAGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

1101 GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1151 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC
GGTAGGTGCG ACAAACTGG AGGTATCTTC TGTGGCCCTG GCTAGGTGCG

1201 TCCGCGGCCG GGAACGGTGC ATTGGAACGC GGATTCCCCG TGCCAAGAGT
AGGCGCCGCG CCTTGCCACG TAACCTTGCG CTAAGGGGC ACGGTTCTCA

1251 GAGATCTGCC ACCATGGCCG GCAAGTGGTC CAAGAGGTCC GTGCCCCGCT
CTCTAGACGG TGGTACCGGC CGTTCACCAG GTTCTCCAGG CACGGGCCGA

1301 GGTCCACCGT GAGGGAGAGG ATGAGGAGGG CCGAGCCCGC CGCCGACAGG
CCAGGTGSCA CTCCTCTCC TACTCCTCCC GGCTCGGGCG GCGGCTGTCC

1351 GTGAGGAGGA CCGAGCCCGC CGCAGTGGGC GTGGGCGCCG TGTCAGGGA
CACTCCTCCT GGCTCGGGCG GCGTCACCCG CACCCGCGGC ACAGGTCCCT

1401 CCTGGAGAAG CACGGCGCCA TCACCTCCTC CAACACCGCC GCCACCAACG
GGACCTCTTC GTGCCGCGGT AGTGGAGGAG GTTGTGGCGG CGGTGTTGC

1451 CCGACTGCGC CTGGCTGGAG GCCCAGGAGG ACGAGGAGGT GGGCTTCCCC
GGGTGACGCG GACCGACCTC CGGGTCTCTC TGCTCCTCCA CCCGAAGGGG

1501 GTGAGGCCCC AGGTGCCCCCT GAGGCCCATG ACCTACAAGG GCGCCGTGGA
CACTCCGGGG TCCACGGGGA CTCGGGTAC TGGATGTTCC CGCGGCACCT

1551 CCTGTCCAC TTCCTGAAGG AGAAGGGCGG CCTGGAGGGC CTGATCCACT
GGACAGGGTG AAGGACTTCC TCTTCCCGCC GGACCTCCCG GACTAGGTGA

1601 CCCAGAAGAG GCAGGACATC CTGGACCTGT GGGTGATCCA CACCCAGGGC
GGGTCTTCTC CGTCTGTAG GACCTGGACA CCCACATGGT GTGGGTCCCG

1651 TACTTCCCCG ACTGGCAGAA CTACACCCCC GGCCCCGGCA TCAGGTTCCT
ATGAAGGGG TGACCGTCTT GATGTGGGGG CCGGGGCCGT AGTCCAAGGG

1701 CCTGACCTTC GGCTGGTGCT TCAAGCTGGT GCCCGTGGAG CCCGAGAAGG
GGACTGGAAG CCGACCACGA AGTTCGACCA CCGGCACCTC GGGTCTTCC

1751 TGGAGGAGGC CAACGAGGGC GAGAACAAC TCGCCGCCCA CCCCATGTCC
ACCTCCTCCG GTTGCTCCCG CTCTTGTGTA CGCGGCGGGT GGGGTACAGG

Figure 27B

1801 CAGCACGGCA T AGGACCC CGAGAAGGAG GTGCTGGAGT GGAGGT SA
 GTCGTGCCGT AGCTCCTGGG GCTCTTCCTC CACGACCTCA CCTCCAAGCT
 1851 CTCCAAGCTG GCCTTCCACC ACGTGGCCAG GGAGCTGCAC CCCGAGTACT
 GAGGTTTCGAC CGGAAGGTGG TGCACCGGTC CCTCGACGTG GGGCTCATGA
 1901 ACAAGGACTG CTAAAGCCCG GGCAGATCTG CTGTGCCTTC TAGTTGCCAG
 TGTTCTCGAC GATTTCCGGC CCGTCTAGAC GACACGGAAG ATCAACGGTC
 1951 CCATCTGTTG TTTGCCCTC CCCCCTGCCT TCCTTGACCC TGGAAGGTGC
 GGTAGACAAC AAACGGGGAG GGGGCACGGA AGGAACTGGG ACCTTCCACG
 2001 CACTCCCCTT GTCTTTCTCT AATAAAATGA GGAAATGCA TCGCATGTGC
 GTGAGGGTGA CAGGAAGGA TTATTTTACT CCTTTAACGT AGCGTAACAG
 2051 TGAGTAGGTG TCATTCTATT CTGGGGGGTG GGGTGGGGCA GGACAGCAAG
 ACTCATCCAC AGTAAGATAA GACCCCCCAG CCCACCCCGT CCTGTCTGTT
 2101 GGGGAGGATT GGAAGACAA TAGCAGGCAT GCTGGGGATG CGGTGGGCTC
 CCCCTCTTAA CCCTTCTGTT ATCGTCCGTA CGACCCCTAC GCCACCCGAG
 2151 TATGGCCGAT CGGCGCGCCG TACTGAAATG TGTGGGCGTG GCTTAAGGGT
 ATACCGGCTA GCCGCGGGC ATGACTTTAC ACACCCGCAC CGAATTCCCA
 2201 GGGAAAGAAT ATATAAGGTG GGGGTCTTAT GTAGTTTGT ATCTGTTTTG
 CCCTTTCTTA TATATTCCAC CCCAGAATA CATCAAAACA TAGACAAAC
 2251 CAGCAGCCGC CGCCGCCATG AGCACCAACT CGTTTGATGG AAGCATGTG
 GTCGTCCGGC GCGGCGGTAC TCGTGGTTGA GCAAACTACC TTCGTAACAC
 2301 AGCTCATATT TGACAACGCG CATGCCCCCA TGGGCCGGGG TCGTCAGAA
 TCGAGTATAA ACTGTTGCGC GTACGGGGGT ACCCGGCCCC ACGCAGTCTT
 2351 TGTGATGGGC TCCAGCATTG ATGGTCGCCC CGTCCTGCCC GCAAACTCTA
 ACACIACCCG AGGTCTGTAAC TACCAGCGGG GCAGGACGGG CGTTTGAGAT
 2401 CTACCTTGAC CTACGAGACC GTGTCTGGAA CGCCGTTGGA GACTGCAGCC
 GATGGAAGTG GATGCTCTGG CACAGACCTT GCGGCAACCT CTGACGTCGG
 2451 TCCGCCGCG CTTCAGCCGC TGCAGCCACC GCCGCGGGA TTGTGACTGA
 AGGCGGCGGC GAAGTCGGCG ACGTCGGTGG CGGGCGCCCT AACACTGACT
 2501 CTTTGCTTTC CTGAGCCCGC TTGCAACAG TGCAGCTTCC CGTTCATCCG
 GAAACGAAAG GACTCGGGCG AACGTTTGTG ACGTCGAAGG GCAAGTAGGC
 2551 CCCGCGATGA CAAGTTGACG GCTCTTTTGG CACAATTGGA TTCTTTGACC
 GGGCGCTACT GTTCAACTGC CGAGAAAACC GTGTTAACCT AAGAACTGG
 2601 CGGGAACCTA ATGTCGTTTC TCAGCAGCTG TTGGATCTGC GCCAGCAGGT
 GCCCTTGAAT TACAGCAAAG AGTCGTCGAC AACCTAGACG CGGTCTGTTA
 2651 TTCTGCCCTG AAGGCTTCCT CCCCTCCCA TCGGTTTAA AACATAAATA
 AAGACGGGAC TTCCGAAGGA GGGGAGGGTT ACGCCAAATT TTGTATTTAT
 2701 AAAAACCAGA CTCTGTTTGG ATTTGGATCA AGCAAGTGTG TTGCTGTCTT
 TTTTGGTCT GAGACAAACC TAAACCTAGT TCGTTCACAG AACGACAGAA

Figure 27C

2751 TATTTAGGGG TTTTGGCGCG GCGGTAGGCC CGGGACCAGC GGTCTCGGTC
 ATAAATCCCC AAAACGCGCG CGCCATCCGG GCCCTGGTCG CCAGAGCCAG
 2801 GTTGAGGGTC CTGTGTATTT TTTCCAGGAC GTGGTAAAGG TGA CTCTGGA
 CAACTCCAG GACACATAAA AAAGGTCCTG CACCATTTC ACTGAGACCT
 2851 TGTCAGATA CATGGGCATA AGCCCGTCTC TGGGGTGGAG GTAGCACCAC
 ACAAGTCTAT GTACCCGTAT TCGGGCAGAG ACCCCACCTC CATCGTGGTG
 2901 TGCAGAGCTT CATGCTGCGG GGTGGTGTG TAGATGATCC AGTCGTAGCA
 ACGTCTCGAA GTACGACGCC CCACCACAAC ATCTACTAGG TCAGCATCGT
 2951 GGAGCGCTGG GCGTGGTGCC TAAAAATGTC TTTCAGTAGC AAGCTGATTG
 CCTCGCGACC CGCACCACGG ATTTTACAG AAAGTCATCG TTCGACTAAC
 3001 CCAGGGGCGAG GCCCTTGGTG TAAGTGTTA CAAAGCGGTT AAGCTGGGAT
 GGTCCTCGTC CGGGAACCAC ATTCACAAAT GTTTCGCCAA TTCGACCCTA
 3051 GGGTGCATAC GTGGGGATAT GAGATGCATC TTGGACTGTA TTTTtaggTT
 CCCACGTATG CACCCCTATA CTCTACGTAG AACCTGACAT AAAAATCCAA
 3101 GGCTATGTTT CCAGCCATAT CCCTCCGGGG ATTCATGTTG TGCAGAACCA
 CCGATACAAG GGTGCGGTATA GGGAGGCCCC TAAGTACAAC ACGTCTTGGT
 3151 CCAGCACAGT GTATCCGGTG CACTTGGGAA ATTTGTCATG TAGCTTAGAA
 GGTGCTGTCA CATAGGCCAC GTGAACCCCT TAAACAGTAC ATCGAATCTT
 3201 GGAAATGCGT GGAAGAACTT GGAGACGCC TGTGACCTC CAAGATTTTC
 CCTTACGCA CCTTCTTGAA CCTCTGCGGG AACACTGGAG GTTCTAAAAG
 3251 CATGCATTCG TCCATAATGA TGGCAATGGG CCCACGGGCG GCGGCTGGG
 GTACGTAAGC AGGTATTACT ACCGTTACCC GGGTGCCCGC GCGCGGACCC
 3301 CGAAGATATT TCTGGGATCA CTAACGTCAT AGTTGTGTTT CAGGATGAGA
 GCTTCTATAA AGACCCTAGT GATTGCAGTA TCAACACAAG GTCTACTCT
 3351 TCGTCATAGG CCATTTTAC AAAGCGCGGG CGGAGGGTGC CAGACTGCGG
 AGCAGTATCC GGTAAAAATG TTTGCGGCC GCCTCCACG GTCTGACGCC
 3401 TATAATGGTT CCATCCGGCC CAGGGGCGTA GTTACCCTCA CAGATTTGCA
 ATATTACCAA GGTAGGCCGG GTCCCCGCAT CAATGGGAGT GTCTAAACGT
 3451 TTTCCACGCG TTTGAGTTCA GATGGGGGGA TCATGTCTAC CTGCGGGGCG
 AAAGGGTGCG AAACCTCAAGT CTACCCCCCT AGTACAGATG GACGCCCCCG
 3501 ATGAAGAAAA CGGTTTCCGG GGTAGGGGAG ATCAGCTGGG AAGAAAGCAG
 TACTTCTTTT GCCAAAGGCC CCATCCCTC TAGTCGACCC TTCTTCGTG
 3551 GTTCTGAGC AGCTGCGACT TACCGCAGCC GGTGGGCCCC TAAATCACAC
 CAAGGACTCG TCGACGCTGA ATGGCGTCGG CCACCCGGGC ATTTAGTGTG
 3601 CTATTACGGG CTGCAACTGG TAGTTAAGAG AGCTGCAGCT GCCGTCATCC
 GATAATGGCC GACGTTGACC ATCAATTCTC TCGACGTCGA CGGCAGTAGG
 3651 CTGAGCAGGG GGGCCACTTC GTTAAGCATG TCCCTGACTC GCATGTTTTT
 GACTCGTCCC CCCGGTGAAG CAATTCGTAC AGGGACTGAG CGTACAAAAG

Figure 27D

3701 CCTGACCAAA TCCAGAA GGCCTCGCC GCCCAGCGAT AGCAGTCT
 GGACTGGTTT AGGCGGTCTT CCGCGAGCGG CGGGTCGCTA TCGTCAAGAA
 3751 GCAAGGAAGC AAAGTTTTTC AACGGTTTGA GACCGTCCGC CGTAGGCATG
 CGTTCCTTCG TTCAAAAAG TTGCCAAACT CTGGCAGGCG GCATCCGTAC
 3801 CTTTTGAGCG TTTGACCAAG CAGTTCCAGG CGGTCCCACA GCTCGGTCAC
 GAAAACTCGC AAAGTGGTTC GTCAAGGTCC GCCAGGGTGT CGAGCCAGTG
 3851 CTGCTCTACG GCATCTCGAT CCAGCATATC TCCTCGTTTC GCGGGTTGGG
 GACGAGATGC CGTAGAGCTA GGTCGTATAG AGGAGCAAAG CGCCCAACCC
 3901 GCGGCTTTTC CTGTACGGCA GTAGTCGGTG CTCGTCCAGA CGGGCCAGGG
 CGCCGAAAGC GACATGCCGT CATCAGCCAC GAGCAGGTCT GCCCGGTCCC
 3951 TCATGTCTTT CCACGGGCGC AGGGTCCTCG TCAGCGTAGT CTGGGTCACG
 AGTACAGAAA GGTGCCCGCG TCCAGGAGC AGTCGCATCA GACCCAGTGC
 4001 GTGAAGGGGT GCGCTCCGGG CTGCGCGCTG GCCAGGGTGC GCTTGAGGCT
 CACTTCCCCA CGCGAGGCCG GACGCGCGAC CGGTCCCACG CGAACTCCGA
 4051 GGTCCTGCTG GTGCTGAAGC GCTGCCGGTC TTCGCCCTGC GCGTCGGCCA
 CCAGGACGAC CACGACTTCG CGACGGCCAG AAGCGGGACG CGCAGCCGGT
 4101 GGTCGATTT GACCATGGTG TCATAGTCCA GCGCTCCGC GGCCTGGCCC
 CCATCGTAAA CTGGTACCAC AGTATCAGGT CGGGGAGGCG CCGCACCAGG
 4151 TTGGCGCGCA GCTTGCCCTT GGAGGAGGCG CCGCAGCAGG GGCAGTGCAG
 AACCAGCGCT CGAACGGGAA CCTCCTCCGC GCGGTGCTCC CCGTCACGTC
 4201 ACTTTTGAGG GCGTAGAGCT TGGGCGCGAG AAATACCGAT TCCGGGGAGT
 TGAAAACCTC CGCATCTCGA ACCCGCGCTC TTTATGGCTA AGGCCCCCTCA
 4251 AGGCATCCGC GCGCAGGCC CCGCAGACGG TCTCGCATTC CACGAGCCAG
 TCCGTAGGCG CGGCGTCCGG GCGGTCTGCC AGAGCGTAAG GTGCTCGGTC
 4301 GTGAGCTCTG GCGGTTCGGG GTCAAAAACC AGGTTTCCCC CATGCTTTTT
 CACTCGAGAC CGCAAGCCC CAGTTTTTGG TCCAAAGGGG GTACGAAAAA
 4351 GATGCGTTTC TTACCTCTGG TTTCCATGAG CCGGTGTCCA CGCTCGGTGA
 CTACGCAAG AATGGAGACC AAAGGTACTC GGCCACAGGT GCGAGCCACT
 4401 CGAAAAGGCT GTCCGTGTCC CCGTATACAG ACTTGAGAGG CCTGTCTCTG
 GCTTTTCCGA CAGGCACAGG GGCATATGTC TGAACCTCTC GGACAGGAGC
 4451 AGCGGTGTTC CGCGGTCTCT CTCGTATAGA AACTCGGACC ACTCTGAGAC
 TCGCCACAAG GCGCCAGGAG GAGCATATCT TTGAGCCTGG TGAGACTCTG
 4501 AAAGGCTCGC GTCCAGGCCA GCACGAAGGA GGCTAAGTGG GAGGGGTAGC
 TTTCCGAGCG CAGGTCCGGT CGTGCTTCCT CCGATTCAAC CTCCCCATCG
 4551 GGTCGTTGTC CACTAGGGGG TCCACTCGCT CCAGGGTGTG AAGACACATG
 CCAGCAACAG GTGATCCCCC AGGTGAGCGA GGTCCCACAC TTCTGTGTAC
 4601 TCGCCCTCTT CGCATCAAG GAAGGTGATT GGTGTGTAGG TGTAGGCCAC
 AGCGGGAGAA GCGTAGTTC CTTCCACTAA CCAAACATCC ACATCCGGTG

Figure 27E

4651 GTGACCGGGT CCTGAAG GGGGGCTATA AAAGGGGGTG GGGGCCCTT
 CACTGGCCCA CAAGGACTTC CCCCCGATAT TTTCCCCCAC CCCCgcgcaa
 4701 CGTCCTCACT CTCTTCCGCA TCGCTGTCTG CGAGGGCCAG CTGTTGGGGT
 GCAGGAGTGA GAGAAGGCGT AGCGACAGAC GCTCCCGGTC GACAACCCCA
 4751 GAGTACTCCC TCTGAAAAGC GGGCATGACT TCTGCGCTAA GATTGTCACT
 CTCATGAGGG AGACTTTTCG CCCGTACTGA AGACGCGATT CTAACAGTCA
 4801 TTCCAAAAAC GAGGAGGATT TGATATTAC CTTGGCCCGCG GTGATGCCTT
 AAGGTTTTTG CTCCTCCTAA ACTATAAGTG GACCGGGCGC CACTACGGAA
 4851 TGAGGGTGGC CGCATCCATC TGGTCAGAAA AGACAATCTT TTTGTTGTCA
 ACTCCCACCG GCGTAGGTAG ACCAGTCTTT TCTGTTAGAA AAACAACAGT
 4901 AGCTTGGTGG CAAACGACCC GTAGAGGGCG TTGGACAGCA ACTTGGCGAT
 TCGAACCACC GTTTGCTGGG CATCTCCCGC AACCTGTCTG TGAACCGCTA
 4951 GGAGCGCAGG GTTTGGTTTT TGTGCGGATC GCGCGCTCC TTGGCCGCGA
 CCTCGCGTCC CAAACCAAAA ACAGCGCTAG CCGCGCGAGG AACCGCGCT
 5001 TGTTTAGCTG CACGTATTCT GCGCAACGC ACCGCCATTG GGGAAAGACG
 ACAAATCGAC GTGCATAAGC GCGGTTGCG TGGCGGTAAG CCTTTCTGCG
 5051 GTGGTGCCTG CGTCGGGCAC CAGGTGCACG CGCCAACCGC GGTGTGTGCG
 CACCACGCGA GCAGCCCGTG GTCCACGTGC GCGGTTGGCG CCAACACGTC
 5101 GGTGACAAAG TCAACGCTGG TGGCTACCTC TCCGCGTAGG CGCTCGTTGG
 CCACTGTTCC AGTTGCGACC ACCGATGGAG AGGCGCATCC GCGACAAACC
 5151 TCCAGCAGAG GCGGCGCCCC TTGCGCGAGC AGAATGGCGG TAGGGGGTCT
 AGGTCGTCTC CGCCGGCGGG AACGCGCTCG TCTTACCGCC ATCCCCAGA
 5201 AGCTGCGTCT CGTCCGGGGG GTCTGCGTCC ACCGTAAAGA CCCCgggCAG
 TCGACGCAGA GCAGGCCCCC CAGACGCAGG TGCCATTTCT GGGGCCCCGTC
 5251 CAGGCGCGCG TCGAAGTAGT CTATCTTGCA TCCTTGCAAG TCTAGCGCCT
 GTCCGCGCGC AGCTTCATCA GATAGAACGT AGGAACGTTT AGATCGCGGA
 5301 GCTGCCATGC GCGGGCGGCA AGCGCGCGCT CGTATGGGTT GAGTGGGGGA
 CGACGGTACG CGCCCGCCGT TCGCGCGCGA GCATACCCAA CTCACCCCT
 5351 CCCCATGGCA TGGGGTGGGT GAGCGCGGAG GCGTACATGC CGCAAATGTC
 GGGGTACCGT ACCCCACCCA CTCGCGCCTC CGCATGTACG GCGTTTACAG
 5401 GTAAACGTAG AGGGGCTCTC TGAGTATTCC AAGATATGTA GGGTAGCATC
 CATTTCATC TCCCCGAGAG ACTCATAAGG TTCTATACAT CCCATCGTAG
 5451 TTCCACCGCG GATGCTGGCG CGCACGTAA TCGTATAGTTC GTGCGAGGGA
 AAGGTGGCGC CTACGACCGC GCGTGCAATTA GCATATCAAG CACGCTCCCT
 5501 GCGAGGAGGT CGGGACCGAG GTTGCTACGG GCGGGCTGCT CTGCTCGGAA
 CGCTCCTCCA GCCCTGGCTC CAACGATGCC CCCCCGACGA GACGAGCCTT
 5551 GACTATCTGC CTGAAGATGG CATGTGAGTT GGATGATATG GTTGGACGCT
 CTGATAGACG GACTTCTACC GTACACTCAA CCTACTATAC CAACCTGCGA

Figure 27F

5601 GGAAGACGTT CTTGGCG TCTGTGAGAC CTACCGCGTC ACGCAO G
 CCTTCTGCAA CTTGACCGC AGACACTCTG GATGGCGCAG TCGTGCTTC
 5651 GAGGCGTAGG AGTCGCGCAG CTTGTTGACC AGCTCGGCGG TGACCTGCAC
 CTCGCGCATCC TCAGCGCGTC GAACAACTGG TCGAGCCGCC ACTGGACGTG
 5701 GTCTAGGGCG CAGTAGTCCA GGGTTTCCTT GATGATGTCA TACTTATCCT
 CAGATCCCGC GTCATCAGGT CCCAAAGGAA CTACTACAGT ATGAATAGGA
 5751 GTCCCTTTTT TTTCCACAGC TCGCGGTTGA GGACAACTC TTCGCGGTCT
 CAGGGAAAAA AAAGGTGTCG AGCGCCAACCT CCTGTTTGAG AAGCGCCAGA
 5801 TTCCAGTACT CTTGGATCGG AAACCCGTCG GCCTCCGAAC GGTAAGAGCC
 AAGGTCATGA GAACCTAGCC TTTGGGCAGC CGGAGGCTTG CCATCTCTCG
 5851 TAGCATGTAG AACTGGTTGA CGGCCTGGTA GGCGCAGCAT CCCTTTTCTA
 ATCGTACATC TTGACCAACT GCCGGACCAT CCGCGTCGTA GGGAAAAGAT
 5901 CGGGTAGCGC GTATGCCTGC GCGGCCTTCC GGAGCGAGGT GTGGGTGAGC
 GCCCATCGCG CATACGGACG CGCCGGAAGG CCTCGCTCCA CACCCACTCG
 5951 GCAAAGGTGT CCCTGACCAT GACTTTGAGG TACTGGTATT TGAAGTCAGT
 CGTTTCCACA GGGACTGGTA CTGAACTCC ATGACCATAA ACTTCAGTCA
 6001 GTCGTCGCAT CCGCCCTGCT CCCAGAGCAA AAAGTCCGTG CGCTTTTGG
 CAGCAGCGTA GCGGGACGA GGGTCTCGTT TTTCAAGCAC CCGAAAAACC
 6051 AACGCGGATT TGGCAGGGCG AAGGTGACAT CGTTGAAGAG TATCTTTCCC
 TTGCGCTAA ACCGTCCCGC TTCCACTGTA GCAACTTCTC ATAGAAAGGG
 6101 GCGCGAGGCA TAAAGTTGCG TGTGATGCGG AAGGGTCCCC GCACCTCGGA
 CGCGCTCCGT ATTTCAACGC ACACTACGCC TTCCAGGGC CGTGGAGCCT
 6151 ACGGTTGTTA ATTACCTGGG CGGCGAGCAC GATCTCGTCA AAGCCGTTGA
 TGCCAAACAAT TAATGGACCC GCCGCTCGTG CTAGAGCAGT TTCGGCAACT
 6201 TGTTGTGGCC CACAATGTAA AGTTCCAAGA AGCGCGGGAT GCCCTTGATG
 ACAACACCGG GTGTTACATT TCAAGGTTCT TCGCGCCCTA CGGGAACCTAC
 6251 GAAGGCAATT TTTAAGTTC CTCGTAGGTG AGCTCTTCAG GGGAGCTGAG
 CTTCGTTAA AAAATTCAAG GAGCATCCAC TCGAGAAGTC CCCTCGACTC
 6301 CCCGTGCTCT GAAAGGGCCC AGTCTGCAAG ATGAGGGTTG GAAGCGACGA
 GGGCACGAGA CTTTCCCGGG TCAGACGTTT TACTCCCAAC CTTGCTGCT
 6351 ATGAGCTCCA CAGGTCACGG GCCATTAGCA TTTGCAGGTG GTCGCGAAAG
 TACTCGAGGT GTCCAGTGCC CGGTAATCGT AAACGTCCAC CAGCGCTTTC
 6401 GTCTTAACT GCGGACCTAT GGCCATTTTT TCTGGGGTGA TGCAGTAGAA
 CAGGATTGTA CCGCTGGATA CCGGTAAAAA AGACCCCACT ACGTCATCTT
 6451 GGTAAGCGGG TCTTGTTCCT AGCGGTCCCA TCCAAGGTTT GCGGCTAGGT
 CCATTCGCCC AGAACAAGGG TCGCCAGGGT AGGTTCCAAG CGCCGATCCA
 6501 CTCGCGCGGC AGTCACTAGA GGTCATCTC CGCCGAACTT CATGACCAGC
 GAGCGCGCCG TCAGTGATCT CCGAGTAGAG GCGGCTTGAA GTACTGGTCG

Figure 27G

6551 ATGAAGGGCA (C)CTGCTT CCCAAAGGCC CCCATCCAAG TATAGG (C)C
 TACTTCCCGT GCTCGACGAA GGGTTTCCGG GGGTAGGTTC ATATCCAGAG
 6601 TACATCGTAG GTGACAAAGA GACGCTCGGT GCGAGGATGC GAGCCGATCG
 ATGTAGCATC CACTGTTTCT CTGCGAGCCA CGCTCCTACG CTCGGCTAGC
 6651 GGAAGAAGTG GATCTCCCGC CACCAATTGG AGGAGTGGCT ATTGATGTGG
 CCTTCTTGAC CTAGAGGGCG GTGGTTAACC TCCTCACCAG TAACTACACC
 6701 TGAAAGTAGA AGTCCCTGCG ACGGGCCGAA CACTCGTGCT GGCTTTTGTA
 ACTTTCATCT TCAGGGACGC TGCCCGGCTT GTGAGCACGA CCGAAACAT
 6751 AAAACGTGCG CAGTACTGGC AGCGGTGCAC GGGCTGTACA TCCTGCACGA
 TTTTGACGCG GTCATGACCG TCGCCACGTG CCCGACATGT AGGACGTGCT
 6801 GGTGACCTG ACGACCGCGC ACAAGGAAGC AGAGTGGGAA TTGAGCCCC
 CCAACTGGAC TGCTGGCGCG GTTCTCTCG TCTCACCCTT AACTCGGGG
 6851 TCGCCTGGCG GGTGCGCTG GTGGTCTTCT ACTTCGGCTG CTGTCTCTTG
 ACGGACCCG CCAAACCGAC CACCAGAAGA TGAAGCCGAC GAACAGGAAC
 6901 ACCGTCTGGC TGCTCGAGGG GAGTTACGGT GGATCGGACC ACCACGCCGC
 TGGCAGACCG ACGAGCTCCC CTCAATGCCA CCTAGCCTCG TGGTGGCGCG
 6951 GCGAGCCCAA AGTCCAGATG TCCGCGCGCG GCGGTCCGAG CTTGATGACA
 CGCTCGGGTT TCAGGTCTAC AGGCGCGCGC CGCCAGCCTC GAACTACTGT
 7001 ACATCGCGCA GATGGGAGCT GTCCATGGTC TGGAGCTCCC GCGGCGTCAG
 TGTAGCGGCT CTACCCTCGA CAGGTACCAG ACCTCGAGGG CGCCGCAGTC
 7051 GTCAGGCGGG AGCTCCTGCA GGTTCACCTC GCATAGACGG GTCAGGGCGC
 CAGTCCGCC TCAGGACGT CCAAATGGAG CGTATCTGCC CAGTCCCGCG
 7101 GGGCTAGATC CAGGTGATAC CTAATTTCCA GGGGCTGGTT GGTGGCGGCG
 CCCGATCTAG GTCCACTATG GATTAAAGGT CCCCAGACAA CCACCGCCGC
 7151 TCGATGGCTT GCAAGAGGCC GCATCCCCGC GCGCGACTA CGGTACCGCG
 AGCTACCGAA CGTCTCCGG CGTAGGGGCG CCGCGCTGAT GCCATGGCGC
 7201 CGGCGGGCGG TGGGCCGCGG GGGTGTCTT GGATGATGCA TCTAAAAGCG
 ,GCCGCCCGCC ACCCGGCGCC CCCACAGGAA CCTACTACGT AGATTTTCGC
 7251 GTGACGCGGG CGAGCCCCCG GAGGTAGGGG GGGCTCCGGA CCCGCCGGGA
 CACTGCGCCC GCTCGGGGCG CTCCATCCCC CCCGAGGCCT GGGCGGCCCT
 7301 GAGGGGGCAG GGGCACGTGC GCGCCGCGCG CGGGCAGGAG CTGGTGCTGC
 CTCCCCCGTC CCCGTGCAGC CGCGGCGCGC GCCCGTCTC GACCACGACG
 7351 GCGCGTAGGT TGCTGGCGAA CGCGACGACG CGGCGGTTGA TCTCCTGAAT
 CGCGCATCCA ACGACCGCTT GCGCTGCTGC GCCGCCAACT AGAGGACTTA
 7401 CTGGCGCCTC TCGGTGAAGA CGACGGGCCC GGTGAGCTTG AACCTGAAAG
 GACCGCGGAG ACGCACTTCT GCTGCCCGGG CCACTCGAAC TTGGACTTTC
 7451 AGAGTTCGAC AGAATCAATT TCGGTGTCGT TGACGGCGGC CTGGCGCAAA
 TCTCAAGCTG TCTTAGTTAA AGCCACAGCA ACTGCCGCGG GACCGCGTTT

Figure 27H

7501 ATCTCCTGCA CCTCCTGA GTTGTCTTGA TAGGCGATTG GGCGCACTAA
 TAGAGGACGT GAGGAGACT CAACAGAACT ATCCGCTAGA GCCGGTCTT
 7551 CTGCTCGATC TCTTCCTCCT GGAGATCTCC GCGTCCGGCT CGCTCCACGG
 GACGAGCTAG AGAAGGAGGA CCTCTAGAGG CGCAGGCCGA GCGAGGTGCC
 7601 TGGCGGCGAG GTCGTTGGAA ATGCGGGCCA TGAGCTGCGA GAAGGCGTTG
 ACCGCCGCTC CAGCAACCTT TACGCCCGGT ACTCGACGCT CTTCCGCAAC
 7651 AGGCCTCCCT CGTTCAGAC GCGGCTGTAG ACCACGCCCC CTTCCGCATC
 TCCGGAGGGA GCAAGGTCTG CGCCGACATC TGGTGGGGG GAAGCCGTAG
 7701 GCGGGCGCGC ATGACCACCT GCGCGAGATT GAGCTCCAGC TGCCGGGCGA
 CGCCCGCGCG TACTGGTGGG CGCGCTCTAA CTCGAGGTGC ACGGCCCGCT
 7751 AGACGGCGTA GTTTCGAGG CGCTGAAAGA GGTAGTTGAG GGTGGTGGCG
 TCTGCCGAT CAAAGCGTCC GCGACTTTCT CCATCAACTC CCACCACCGC
 7801 GTGTGTTCTG CCACGAAGAA GTACATAACC CAGCGTCGCA ACGTGGATTC
 CACACAAGAC GGTGCTTCTT CATGTATTGG GTCGCAGCGT TGCACCTAAG
 7851 GTTGATATCC CCCAAGGCCT CAAGGCGCTC CATGGCCTCG TAGAAGTCCA
 CAACTATAGG GGGTTCGGGA GTTCCGCGAG GTACCGGAGC ATCTTCAGST
 7901 CGGCGAAGTT GAAAACTGG GAGTTGCGCG CCGACACGGT TAACTCCTCC
 GCCGCTTCAA CTTTTTGACC CTCAACGCGC GGCTGTGCCA ATTGAGGAGG
 7951 TCCAGAAGAC GGATGAGCTC GGCACAGTG TCGCGCACCT CGCGCTCAAA
 AGSTCTTCTG CCTACTCGAG CCGCTGTAC AGCGCGTGGA GCGCGAGTTT
 8001 GGCTACAGGG GCCTCTTCTT CTTCTTCAAT CTCCTCTTCC ATAAGGGCCT
 CCGATGTCCC CGGAGAAGAA GAAGAAGTTA GAGGAGAAGG TATTCCTCGA
 8051 CCCCTTCTTC TTCTTCTGGC GCGGTGGGG GAGGGGGGAC ACGGCGGCGA
 GGGGAAGAAG AAGAAGACCG CCGCCACCCC CTCCTCCCTG TGCCGCCGCT
 8101 CGACGGCGCA CCGGAGGCG GTCGACAAAG CGCTCGATCA TCTCCCCGCG
 GCTGCCGCGT GGCCCTCCGC CAGCTGTTTC GCGAGCTAGT AGAGGGGCGC
 8151 GCGACGGCGC ATGCTCTCGG TGACGGCGCG GCCGTCTCG CGGGGGCGCA
 CGCTGCCGCG TACCAGAGCC ACTGCCGCGC CGGCAAGAGC GCGCCCGCT
 8201 GTTGAAGAC GCCGCCGCTC ATGTCCCGGT TATGGGTTGG CGGGGGGCTG
 CAACCTTCTG CGGCGGGCAG TACAGGGCCA ATACCCAACC GCGCCCGGAC
 8251 CCATGCGGCA GGGATACGGC GCTAACGATG CATCTCAACA ATTGTTGTGT
 GGTACGCCGT CCCTATGCCG CGATTGCTAC GTAGAGTTGT TAACAACACA
 8301 AGGTACTCCG CCGCCGAGGG ACCTGAGCGA GTCCGCATCG ACCGGATCGG
 TCCATGAGGC GCGGGCTCCC TGGACTCGCT CAGGCGTAGC TGGCCTAGCC
 8351 AAAACCTCTC GAGAAAGGCG TCTAACCACT CACAGTCGCA AGGTAGGCTG
 TTTTGGAGAG CTCTTTCCGC AGATTGCTCA GTGTCAGCGT TCCATCCGAC
 8401 AGCACCGTGG CGGGCGGCG CGGGCGGCGG TCGGGGTTGT TTCTGGCGGA
 TCGTGGCACC GCCCGCGCTC GCGCGCGGCC AGCCCAACA AAGACCGCCT

Figure 27I

8451 GGTGCTGCTG AATGTAAT TAAAGTAGGC GGTCTTGAGA CGGCGGCG
 CCACGACGAC TACTACATTA ATTTTCATCCG CCAGAACTCT GCCGCCTACC
 8501 TCGACAGAAG CACCATGTCC TTGGGTCCGG CCTGCTGAAT GCGCAGGCGG
 AGCTGTCTTC GTGGTACAGG AACCCAGGCC GGACGACTTA CGCGTCCGCC
 8551 TCGGCCATGC CCCAGGCTTC GTTTTGACAT CGGCGCAGGT CTTTGTAAGTA
 AGCCGGTACG GGGTCCGAAG CAAAACGTGA GCCGCGTCCA GAAACATCAT
 8601 GTCTTGATG AGCCTTTCTA CCGGCACTTC TTCTTCTCCT TCCTCTGTGTC
 CAGAACGTAC TCGGAAGAT GGCCGTGAAG AAGAAGAGGA AGGAGAACAG
 8651 CTGCATCTCT TGCATCTATC GCTGCGGCGG CGGCGGAGTT TGCCCGTAGG
 GACGTAGAGA ACGTAGATAG CGACGCCGCC GCCGCCTCAA ACCGGCATCC
 8701 TGGCGCCCTC TTCCTCCCAT GCGTGTGACC CCGAAGCCCC TCATCGGCTG
 ACCGCGGGAG AAGGAGGGTA CGCACACTGG GGCTTCGGGG AGTAGCCGAC
 8751 AAGCAGGGCT AGGTCCGCGA CAACCGCTC GGCTAATATG GCCTGCTGCA
 TTCGTCCCGA TCCAGCCGCT GTTGCAGGAG CCGATTATAC CGGACGACGT
 8801 CCTGCGTGAG GGTAGACTGG AAGTCATCCA TGTCACAAA GCGGTGGTAT
 GGACGCACTC CCATCTGACC TTCAGTAGGT ACAGGTGTTT CGCCACCATA
 8851 GCGCCCGTGT TGATGGTGTG AGTGCACTG GCCATAACGG ACCAGTTAAC
 CCGGGGCACA ACTACCACAT TCACGTCAAC CGGTATTGCC TGGTCAATTG
 8901 GGTCTGGTGA CCCGGCTGCG AGAGCTCGGT GTACCTGAGA CGCGAGTAAG
 CCAGACCACT GGGCCGACGC TCTCGAGCCA CATGGACTCT GCGCTCATTC
 8951 CCCTCGAGTC AAATACGTAG TCGTTGCAAG TCCGCACCAG GTACTGGTAT
 GGGAGCTCAG TTTATGCATC AGCAACGTTT AGGCGTGGTC CATGACCATA
 9001 CCCACCAAAA AGTGCGGCGG CGGCTGGCGG TAGAGGGGCC AGCGTAGGGT
 GGGTGGTTTT TCACGCCGCC GCCGACGCC ATCTCCCCGG TCGCATCCCA
 9051 GGCCGGGGCT CCGGGGGCGA GATCTTCCAA CATAAGGCGA TGATATCCGT
 CCGGCCCGCA GGGCCCCGCT CTAGAAGGTT GTATTCCGCT ACTATAGGCA
 9101 AGATGTACCT GGACATCCAG GTGATGCCGG CGGCGGTGGT GGAGGCGCGC
 TCTACATGGA CCTGTAGGTC CACTACGGCC GCCGCCACCA CCTCCGCGCG
 9151 GGAAAGTCGC GGACGCGGTT CCAGATGTTG CGCAGCGGCA AAAAGTGCTC
 CCTTTCAGCG CCTGCGCCAA GGTCTACAA GCGTCGCCGT TTTTCACGAG
 9201 CATGGTCCGG ACGCTCTGGC CGGTCAGGCG CGGCAATCG TTGACGCTCT
 GTACCAGCCC TGCAGAGCCG GCCAGTCCGC GCGCGTTAGC AACTGCGAGA
 9251 AGACCGTGCA AAAGGAGAGC CTGTAAGCGG GCACTCTTCC GTGGTCTGGT
 TCTGGCACGT TTTCTCTCG GACATTCGCC CGTGAGAAGG CACCAGACCA
 9301 GGATAAATTC GCAAGGGTAT CATGGCGGAC GACCGGGGTT CGAGCCCCGT
 CCTATTTAAG CGTTCACATA GTACCGCCTG CTGGCCCCAA GCTCGGGGCA
 9351 ATCCGGCCGT CCGCCGTGAT CCATGCGGTT ACCGCCCGCG TGTCGAACCC
 TAGGCCGGCA GCGGCGACTA GGTACGCCAA TGGCGGGCGC ACAGCTTGGG

Figure 27J

9401 AGGTGTGCGA CAGACAA CGGGGAGTG CTCCTTTTGG CTTCCCTA
TCCACACGCT GCAGTCTGTT GCCCCTCAC GAGGAAAACC GAAGGAAGGT

9451 GGC GCGCGG CTGCTGCGCT AGCTTTTTTG GCCACTGGCC GCGCGCAGCG
CCGCGCCGCC GACGACGCGA TCGAAAAAC CCGTGACCGG CCGCGCTCGC

9501 TAAGCGGTGA GGCTGGAAAG CGAAAGCATT AAGTGCTCG CTCCTGTAG
ATTCGCCAAT CCGACCTTTC GCTTTCGTAA TTCACCGAGC GAGGGACATC

9551 CCGGAGGGTT ATTTTCCAAG GGTGAGTCG CGGGACCCCC GGTTCGAGTC
GGCCTCCCAA TAAAAGGTTT CCAACTCAGC GCCCTGGGG CCAAGCTCAG

9601 TCGGACCGGC CGGACTGCGG CGAACGGGGG TTTGCCTCCC CGTCATGCAA
AGCCTGGCCG GCCTGACGCC GCTTGCCCC AAACGGAGGG GCAGTACGTT

9651 GACCCCGCTT GCAAATTCCT CCGGAAACAG GGACGAGCCC CTTTTTTGCT
CTGGGGCGAA CGTTTAAGGA GGCTTTGTC CCTGCTCGGG GAAAAACGA

9701 TTTCCAGAT GCATCCGGTG CTGCGGCAGA TGCGCCCCC TCCTCAGCAG
AAAGGTCTA CGTAGGCCAC GACGCCGTCT ACGCGGGGG AGGAGTCGT

9751 CGGCAAGAGC AAGAGCAGCG GCAGACATGC AGGGCACCCCT CCCCTCCTCC
GCCGTCTCG TTCTCGTCGC CGTCTGTACG TCCCGTGGGA GGGGAGGAG

9801 TACCGCGTCA GGAGGGGCGA CATCCCGGT TGACGCGCA GCAGATGGTG
ATGGCGCAGT CCTCCCGCT GTAGGCGCA ACTGCGCGT CGTCTACCAC

9851 ATTACGAACC CCCGCGCGC CGGGCCCGC ACTACCTGGA CTTGGAGGAG
TAATGCTTGG GGGCGCCGC GCCCGGCCG TGATGGACCT GAACCTCCTC

9901 GCGGAGGGCC TGGCGCGGT AGGAGCGCC TCTCTGAGC GGCACCAAG
CCGTCCCGG ACCGCGCCGA TCCTCGCGG AGAGGACTCG CCGTGGGTT

9951 GGTGCAGCTG AAGCGTGATA CGCGTGAGGC GTACGTGCCG CGGCAGAACC
CCACGTGAC TTCGCACTAT GCGCACTCCG CATGCACGGC GCCGTCTTGG

10001 TGTTTCGCGA CCGCGAGGGA GAGGAGCCCG AGGAGATGCG GGATCGAAAG
ACAAAGCGCT GCGCTCCCT CTCCTCGGGC TCCTCTACGC CCTAGCTTTC

10051 TTCCACGAG GCGCGAGCT GCGGCATGGC CTGAATCGCG AGCGTTGCT
AAGGTGCGTC CCGCGCTCGA CGCCGTACCG GACTTAGCGC TCGCCAACGA

10101 GCGCGAGGAG GACTTTGAGC CCGACGCGC AACC GGATT AGTCCCGCGC
CGCGCTCCTC CTGAAACTCG GGCTGCGCGC TTGGCCCTAA TCAGGGCGCG

10151 GCGCACACGT GCGGCGGCC GACCTGGTAA CCGCATACGA GCAGACGGTG
CGCGTGTGCA CCGCGCGCG CTGGACCATT GCGGTATGCT CGTCTGCCAC

10201 AACCAGGAGA TTAACTTTCA AAAAGCTTT AACAACCAG TCGGTACGCT
TTGGTCTCT AATTGAAAGT TTTTTCGAAA TTGTGTTGTC ACGCATGCGA

10251 TGTGGCGCGC GAGGAGGTGG CTATAGGACT GATGCATCTG TGGGACTTTG
ACACCGCGCG CTCCTCCACC GATATCCTGA CTACGTAGAC ACCCTGAAAC

10301 TAAGCGCGCT GGAGCAAAAC CCAAATAGCA AGCCGCTCAT GCGCGAGCTG
ATTCGCGCGA CCTCGTTTTG GGTATTATCGT TCGGCGAGTA CCGCGTCGAC

Figure 27K

10351 TTCCTTATAG TGCACAG CAGGGACAAC GAGGCATTCA GGGATG T
 AAGGAATATC ACCTCGTGTC GTCCCTGTTG CTCCGTAAGT CCCTACGGA
 10401 GCTAAACATA GTAGAGCCCG AGGGCCGCTG GCTGCTCGAT TTGATAAACA
 CGATTTGTAT CATCTCGGGC TCCCGGCGAC CGACGAGCTA AACTATTTGT
 10451 TCCTGCAGAG CATAGTGGTG CAGGAGCGCA GCTTGAGCCT GGCTGACAAG
 AGGACGTCTC GTATCACCAC GTCCTCGCGT CGAACTCGGA CCGACTGTTC
 10501 GTGGCCGCCA TCAACTATTC CATGCTTAGC CTGGGCAAGT TTTACGCCCG
 CACCGGCGGT AGTTGATAAG GTACGAATCG GACCCGTTCA AAATGCGGGC
 10551 CAAGATATAC CATACCCTT ACGTCCCAT AGACAAGGAG GTAAAGATCG
 GTTCTATATG GTATGGGGA TGAAGGGTA TCTGTTCTC CATTCTAGC
 10601 AGGGGTTCTA CATGCGCATG GCGCTGAAGG TGCTTACCTT GAGCGACGAC
 TCCCCAAGAT GTACCGGTAC CGCGACTTCC ACGAATGGAA CTCGCTGCTG
 10651 CTGGGCGTTT ATCGCAACGA GCGCATCCAC AAGGCCGTGA GCGTGAGCCG
 GACCCGCAAA TAGCGTTGCT CGCGTAGGTG TTCCGGCACT CGCACTCGGC
 10701 GCGGCGCGAG CTCAGCGACC GCGAGCTGAT GCACAGCCTG CAAAGGGCCC
 CGCCGCGCTC GAGTCGCTGG CGCTCGACTA CGTGTGCGAC GTTTCCCGGG
 10751 TGGCTGGCAC GGGCAGCGGC GATAGAGAGG CCGAGTCTTA CTTTGACGCG
 ACCGACCGTG CCCGTCGCCG CTATCTCTCC GGCTCAGGAT GAAACTGCGC
 10801 GCGGCTGACC TGGCTGGGC CCCAAGCCGA CGCGCCCTGG AGGCAGCTGG
 CCGCGACTGG ACGCGACCCG GGGTTCGGCT GCGCGGGACC TCCGTCGACC
 10851 GGCCGGACCT GGGCTGGCGG TGGCACCCGC GCGCGTGGC AACGTCGGCG
 CCGGCCCTGA CCCGACGCC ACCGTGGCG GCGCGACCG TTGCAGCCGC
 10901 GCGTGGAGGA ATATGACGAG GACGATGAGT ACGAGCCAGA GGACGGCGAG
 CGCACCTCT TATACTGCTC CTGCTACTCA TGCTCGGTCT CCTGCCGCTC
 10951 TACTAAGCGG TGATGTTTCT GATCAGATGA TGCAAGACGC AACGGACCCG
 ATGATTCGCC ACTACAAAGA CTAGTCTACT ACGTTCGTGG TTGCCTGGGC
 11001 GCGGTGCGGG CGGCGCTGCA GAGCCAGCCG TCCGGCCTTA ACTCCACGGA
 CGCCACGCCC GCGCGACGT CTCGGTCGGC AGGCCGGAAT TGAGGTGCCT
 11051 CGACTGGCGC CAGGTCATGG ACCGCATCAT GTCGCTGACT GCGCGCAATC
 GCTGACCGCG GTCCAGTACC TGGCGTAGTA CAGCGACTGA CGCGCGTTAG
 11101 CTGACGCGTT CCGGCAGCAG CCGCAGGCCA ACCGGCTCTC CGCAATTCTG
 GACTGCGCAA GCGCGTCGTC GCGTCCGGT TGGCCGAGAG GCGTTAAGAC
 11151 GAAGCGGTGG TCCCGGCGCG CGCAAACCCC ACGCACGAGA AGGTGCTGGC
 CTCGCCACC AGGGCCGCGC GCGTTTGGGG TCGTGCTCT TCCACGACCG
 11201 GATCGTAAAC GCGCTGGCCG AAAACAGGGC CATCCGGCCC GACGAGGCCG
 CTAGCATTTG CCGGACCGGC TTTTGTCCCG GTAGGCCGGG CTGCTCCGGC
 11251 GCCTGGTCTA CGACGCGCTG CTTGAGCGCG TGGCTCGTTA CAACAGCGGC
 CGGACCAGAT GCTGCGCGAC GAAGTCGCGC ACCGAGCAAT GTTGTGCGCG

Figure 27L

11301 AACGTGCAGA CCTGGA CCGGCTGGTG GGGGATGTGC GCGAGG T
 TTGCACGTCT GGTGGACCT GGCCGACCAC CCCCTACACG CGCTCCGCA
 11351 GGGCGAGCGT GAGCGCGCGC AGCAGCAGGG CAACCTGGGC TCCATGGTTG
 CCGCGTCGCA CTCGCGCGCG TCGTCGTCCC GTTGGACCCG AGGTACCAAC
 11401 CACTAAACGC CTTCTGAGT ACACAGCCCG CCAACGTGCC GCGGGGACAG
 GTGATTTGCG GAAGGACTCA TGTGTCGGGC GGTGACACGG CGCCCTGTG
 11451 GAGGACTACA CCAACTTTGT GAGCGCACTG CCGCTAATGG TGACTGAGAC
 CTCCTGATGT GGTGAAACA CTCGCGTGAC GCCGATTACC ACTGACTCTG
 11501 ACCGCAAAAGT GAGGTGTACC AGTCTGGGCC AGACTATTTT TTCCAGACCA
 TGCGTTTCA CTCCACATGG TCAGACCCGG TCTGATAAAA AAGGTCTGGT
 11551 GTAGACAAGG CCTGCAGACC GTAAACCTGA GCCAGGCTTT CAAAACTTG
 CATCTGTTCC GGACGTCTGG CATTGGAAT CCGTCCGAAA GTTTTGAAC
 11601 CAGGGGCTGT GGGGGGTGCG GGCTCCACA GCGGACCGCG CGACCGTGTG
 GTCCCCGACA CCCCCACGC CCGAGGGTGT CCGCTGGCGC GCTGGCACAG
 11651 TAGCTTGCTG ACGCCCAACT CGCGCTGTT GCTGCTGCTA ATAGCGCCCT
 ATCGAACGAC TCGGGTTGA GCGCGGACAA CGACGACGAT TATCGCGGGA
 11701 TCACGACAG TGGCAGCGTG TCCCGGACA CATACTAGG TCACTTGCTG
 AGTGCTGTG ACCGTCGCAC AGGGCCCTGT GTATGGATCC AGTGAACGAC
 11751 ACACTGTACC GCGAGGCCAT AGGTCAGGCG CATGTGGACG AGCATACTTT
 TGTGACATGG CGCTCCGTA TCCAGTCCGC GTACACCTGC TCGTATGAAA
 11801 CCAGGAGATT ACAAGTGTA GCCGCGCGCT GGGGAGGAG GACACGGGCA
 GGTCTCTAA TGTTCACAGT CGGCGCGCGA CCCCCTCCTC CTGTGCCCGT
 11851 GCCTGGAGGC AACCTAAAC TACCTGCTGA CCAACCGGCG GCAGAAGATC
 CGGACCTCCG TTGGGATTG ATGGACGACT GGTGGCCGC CGTCTTCTAG
 11901 CCCTCGTTGC ACAGTTTAA CAGCGAGGAG GAGCGCATTT TGCGCTACGT
 GGGAGCAACG TGTCAAATTT GTCGCTCCTC CTCGCGTAAA ACSCGATGCA
 11951 GCAGCAGAGC GTGAGCCTTA ACCTGATGCG CGACGGGTA ACGCCCAGCG
 CGTCGTCTCG CACTCGGAAT TGGACTACGC GCTGCCCCAT TGCGGGTCCG
 12001 TGGCGCTGGA CATGACCGCG CGCAACATGG AACCGGGCAT GTATGCCTCA
 ACCGCGACCT GTACTGGCGC GCGTTGTACC TTGGCCCGTA CATACTGAGT
 12051 AACC GGCCGT TTATCAACCG CCTAATGGAC TACTTGCAAT GCGCGGCCG
 TTGGCCGGCA AATAGTTGGC GGATTACCTG ATGAACGTAG CGCGCCGGCG
 12101 CGTGAACCCC GAGTATTCA CCAATGCCAT CTTGAACCCG CACTGGCTAC
 GCAC TTGGGG CTCATAAAGT GGTACGGTA GAACTTGGGC GTGACCGATG
 12151 CGCCCCCTGG TTTCTACACC GGGGGATTG AGGTGCCCCA GGGTAACGAT
 GCGGGGGACC AAAGATGTGG CCCCCAAGC TCCACGGGCT CCCATTGCTA
 12201 GGATTCCTCT GGGACGACAT AGACGACAGC GTGTTTCCC CGCAACCGCA
 CCTAAGGAGA CCCTGCTGTA TCTGCTGTCG CACAAAAGG GCGTTGGCGT

Figure 27 M

12251 GACCCCTGCTA GATTGCAAC AGCGCGAGCA GGCAGAGGCG GCGCTCTGCA
 CTGGGACGAT CAAACGTIG TCGCGCTCGT CCGTCTCCGC CGCGACCTT
 12301 AGGAAAGCTT CCGCAGGCCA AGCAGCTTGT CCGATCTAGG CGCTGCGGCC
 TCCTTTTCGAA GCGGTCCGGT TCGTCGAACA GGCTAGATCC GCGACGCCGG
 12351 CCGCGGTGAG ATGCTAGTAG CCCATTTCCTA AGCTTGATAG GGTCTCTTAC
 GCGCCAGTC TACGATCATC GGGTAAAGGT TCGAACTATC CCAGAGAATG
 12401 CAGCACTCGC ACCACCCGCC CGCGCCTGCT GGGCGAGGAG GAGTACCTAA
 GTCGTGAGCG TGGTGGGCGG GCGCGGACGA CCCGCTCCTC CTCATGGATT
 12451 ACAACTCGCT GCTGCAGCCG CAGCGCGAAA AAAACCTGCC TCCGGCATTT
 TGTGAGCGA CGACGTCCGC GTCGCGCTTT TTTTGGACGG AGGCCGTAAA
 12501 CCCAACACG GGATAGAGAG CCTAGTGGAC AAGATGAGTA GATGGAAGAC
 GGTTTGTTC CCTATCTCTC GGATCACCTG TTCTACTCAT CTACCTTCTG
 12551 GTACGCGCAG GAGCACAGGG ACGTCCAGG CCCGCGCCCG CCCACCCGTC
 CATGCGCGTC CTCGTGTCCC TGCACGGTCC GGGCGCGGGC GGGTGGGCAG
 12601 GTCAAAGGCA CGACCGTCAG CGGGGTCTGG TGTGGGAGGA CGATGACTCG
 CAGTTTCCGT GCTGGCAGTC GCCCCAGACC ACACCTCCT GCTACTGAGC
 12651 GCAGACGACA GCAGCGTCCT GGATTGCGGA GGGAGTGGCA ACCCGTTTGC
 CGTCTGCTGT CGTCGCAGGA CCTAAACCCT CCCTCACCCT TGGGCAACG
 12701 GCACCTTCGC CCCAGGCTGG GGAGAATGTT TTAAAAAAA AAAAAGCATG
 CGTGGAAGCG GGGTCCGACC CCTCTTACAA AATTTTTTTT TTTTTCGTAC
 12751 ATGCAAAATA AAAAATCAC CAAGGCCATG GCACCGAGCG TTGGTTTCT
 TACGTTTTAT TTTTGTAGTG GTCCGGTAC CGTGGCTCGC AACCAAAAGA
 12801 TGTATTCCCC TTAGTATGCG GCGCGCGGCG ATGTATGAGG AAGGTCTCC
 ACATAAGGGG AATCATAACG CCGCGCCGCG TACATACTCC TTCCAGGAGG
 12851 TCCCTCCTAC GAGAGTGTGG TGAGCGCGGC GCCAGTGGCG GCGCGCTGG
 AGGAGGATG CTCTCACACC ACTCGCGCGC CGGTACCGC GCGCGGACC
 12901 GTTCTCCCTT CGATGCTCCC CTGGACCCGC CGTTGTGCC TCCGCGGTAC
 CAAGAGGGAA GCTACGAGGG GACCTGGGCG GCAAACACGG AGGCGCCATG
 12951 CTGCGGCCTA CCGGGGGGAG AAACAGCATC CGTACTCTG AGTTGGCACC
 GACGCCGGAT GGGCCCCCTC TTTGTCTAG GCAATGAGAC TCAACCGTGG
 13001 CCTATTCGAC ACCACCCGTG TGTACCTGGT GGACAACAAG TCAACGGATG
 GGATAAGCTG TGGTGGGCAC ACATGGACCA CTTGTTGTTC AGTTGCCTAC
 13051 TGGCATCCCT GAACTACCAG AACGACCACA GCAACTTTCT GACCACGGTC
 ACCGTAGGGA CTTGATGGTC TTGCTGGTGT CGTTGAAAGA CTGGTGCCAG
 13101 ATTCAAAACA ATGACTACAG CCCGGGGGAG GCAAGCACAC AGACCATCAA
 TAAGTTTTGT TACTGATGTC GGGCCCCCTC CGTTCGTGTG TCTGGTAGTT
 13151 TCTTGACGAC CGGTGCGACT GGGGCGGCGA CCTGAAAACC ATCCTGCATA
 AGAACTGCTG GCCAGCGTGA CCCGCGCGCT GGACTTTTGG TAGGACGTAT

Figure 27N

13201 CCAACATGCC AATGTGAAC GAGTTCATGT TTACCAATAA GTTTAAAGG
 GGTGTACGG TCACTTG CTCAAGTACA AATGGTTATT CAAATTG C
 13251 CGGGTGATGG TGTCGCGCTT GCCTACTAAG GACAATCAGG TGGAGCTGAA
 GCCCACTACC ACAGCGCGAA CGGATGATTC CTGTTAGTCC ACCTCGACTT
 13301 ATACGAGTGG GTGGAGTTCA CGCTGCCCCG GGGCAACTAC TCCGAGACCA
 TATGCTCACC CACCTCAAGT GCGACGGGCT CCCGTTGATG AGGCTCTGGT
 13351 TGACCATAGA CCTTATGAAC AACGCGATCG TGGAGCACTA CTTGAAAGTG
 ACTGGTATCT GGAATACTTG TTGCGCTAGC ACCTCGTGAT GAACTTTCAC
 13401 GGCAGACAGA ACGGGGTCTT GGAAAGCGAC ATCGGGGTAA AGTTTGACAC
 CCGTCTGTCT TGCCCCAAGA CCTTTCGCTG TAGCCCCATT TCAAAGTGTG
 13451 CCGCAACTTC AGACTGGGGT TTGACCCCGT CACTGGTCTT GTCATGCCTG
 GCGGTTGAAG TCTGACCCCA AACTGGGGCA GTGACCAGAA CAGTACGGAC
 13501 GGGTATATAC AAACGAAGCC TTCCATCCAG ACATCATTTT GCTGCCAGGA
 CCGATATATG TTTGCTTCGG AAGGTAGGTC TGTAGTAAAA CGACGGTCCT
 13551 TGCGGGGTGG ACTTCACCCA CAGCCGCTG AGCAACTTGT TGGGCATCCG
 ACGCCACC TGAAGTGGGT GTCGGCGGAC TCGTTGAACA ACCCGTAGGC
 13601 CAAGCGGCAA CCCTTCCAGG AGGGCTTTAG GATCACCTAC GATGATCTGG
 GTTCGCCGTT GGAAGGTCC TCCGAAATC CTAGTGGATG CTACTAGACC
 13651 AGGGTGGTAA CATTCGCCA CTGTTGGATG TGGACGCTA CCAGGCGAGC
 TCCACCAT TGAAGGGCGT GACAACCTAC ACCTGCGGAT GGTCCGCTCG
 13701 TTGAAAGATG ACACCGAACA GGGCGGGGGT GCGCGAGGCG GCAGCAACAG
 AACTTTCTAC TGTGGCTTGT CCGCCCCCA CCGCGTCCGC CGTCGTTGTC
 13751 CAGTGGCAGC GCGCGGAAG AGAACTCCAA CCGCGCAGCC GCGCAATGC
 GTACCCGTCG CCGCGCCTTC TCTTGAGGT GCGCCGTCG GCGCGTTACG
 13801 AGCCGGTGGA GGACATGAAC GATCATGCCA TTCGCGGCGA CACCTTTGCC
 TCGGCCACCT CCTGTACTTG CTAGTACGGT AAGCGCGCT GTGGAACGG
 13851 ACACGGGCTG AGGAGAAGCG CGCTGAGGCC GAAGCAGCGG CCGAAGCTGC
 TGTGCCCCGAC TCCTCTTCGC GCGACTCCG CTTCGTCGCC GGCTTCGACG
 13901 CGCCCCCGCT GCGCAACCCG AGGTCGAGAA GCCTCAGAAG AAACCGGTGA
 GCGGGGCGA CCGGTTGGGC TCCAGCTCTT CCGAGTCTTC TTTGGCCACT
 13951 TCAAACCCCT GACAGAGGAC AGCAAGAAAC GCAGTTACAA CCTAATAAGC
 AGTTTGGGGA CTGTCTCCTG TCGTCTTTG CGTCAATGTT GGATTATTG
 14001 AATGACAGCA CCTTCACCCA GTACCGCAGC TGGTACCTTG CATACACTA
 TTACTGTCGT GGAAGTGGGT CATGGCGTCG ACCATGGAAC GTATGTTGAT
 14051 CCGCGACCCCT CAGACCGGAA TCCGCTCATG GACCCTGCTT TGCACTCCTG
 GCCGCTGGGA GTCTGGCCTT AGGCGAGTAC CTGGGACGAA ACGTGAGGAC
 14101 ACGTAACCTG CCGCTCGGAG CAGGTCTACT GGTGCTTGC AGACATGATG
 TGCATTGGAC GCCGAGCCTC GTCCAGATGA CCAGCAACGG TCTGTACTAC

Figure 270

14151 CAAGACCCCG TTTTCCG CTCCACGCGC CAGATCAGCA ACTTTC
 GTTCTGGGGC ACTGGAAGGC GAGGTGCGCG GTCTAGTCGT TGAAAGGCCA
 14201 GGTGGGCGCC GAGCTGTTGC CCGTGCACTC CAAGAGCTTC TACAACGACC
 CCACCCGCGG CTCGACAACG GGCACGTGAG GTTCTCGAAG ATGTTGCTGG
 14251 AGGCCGTCTA CTCCCAACTC ATCCGCCAGT TTACCTCTCT GACCCACGTG
 TCCGCGAGAT GAGGTTGAG TAGGCGCTCA AATGGAGAGA CTGGGTGCAC
 14301 TTCAATCGCT TTCCCGAGAA CCAGATTTTG GCGCGCCCGC CAGCCCCCAC
 AAGTTAGCGA AAGGGCTCTT GGTCTAAAAC CCGCGGGCGG GTCGGGGGTG
 14351 CATCACCACC GTCAGTGAAA ACGTTCCTGC TCTCACAGAT CACGGGACGC
 GTAGTGGTGG CAGTCACTTT TGCAAGGACG AGAGTGCTTA GTGCCCTGCG
 14401 TACCGCTGCG CAACAGCATC CGAGGAGTCC ACGAGTGAC CATTACTGAC
 ATGGCGACGC GTTGTCTAG CCTCCTCAGG TCGCTCACTG GTAATGACTG
 14451 GCCAGACGCC GCACCTGCCC CTACGTTTAC AAGGCCCTGG GCATAGTCTC
 CGGTCTGCGG CGTGSACGGG GATGCAAATG TTCCGGGACC CGTATCAGAG
 14501 GCGCGCGGTC CTATCGAGCC GCACTTTTTG AGCAAGCATG TCCATCCTTA
 CGCGCGCAG GATAGCTCGG CGTGAAAAC TCGTTCGTAC AGGTAGGAAT
 14551 TATCGCCAG CAATAACACA GGCTGGGGCC TCGCTTCCC AAGCAAGATG
 ATAGCGGGTC GTTATTGTGT CCGACCCCGG ACGCGAAGGG TTCGTTCTAC
 14601 TTTGGCGGGG CCAAGAAGCG CTCCGACCAA CACCCAGTGC GCGTGC GCGG
 AAACCGCCCC GGTCTTTCGC GAGGCTGGTT GTGGGTCACG CGCACGCGCC
 14651 GCACTACCGC GCGCCCTGGG GCGCGCACA ACGCGGCCGC ACTGGGCGCA
 CGTGATGGCG CGCGGGACCC CGCGCTGT TCGCGCGGCG TGACCCGCGT
 14701 CCACCGTCGA TGACGCCATC GACGCGGTGG TGGAGGAGGC GCGCAACTAC
 GGTGGCAGCT ACTGCGGTAG CTGCGCCACC ACCTCCTCCG CGCGTTGATG
 14751 ACGCCACGCG CGCCACCACT GTCCACAGTG GACGCGGCCA TTCAGACCGT
 TCGGGGTGCG GCGGTGGTCA CAGGTGTCAC CTGCGCCGGT AAGTCTGGCA
 14801 GGTGCGCGGA GCCCGGCGCT ATGCTAAAAT GAAGAGACGG CGGAGGCGCG
 CCACGCGCCT CGGGCCGCGA TACGATTTTA CTTCTCTGCC GCCTCCGCGC
 14851 TAGCACGTCG CCACCGCCGC CGACCCGGCA CTGCCGCCA ACGCGCGGCG
 ATCGTGACAGC GGTGGCGGCG GCTGGGCCGT GACGCGGGT TCGCGCGCGC
 14901 GCGGCCCTGC TTAACCGCGC ACGTCGCACC GGCCGACGGG CGGCCATGCG
 CGCCGGGACG AATTGGCGCG TGCAGCGTG CGGCTGCC CCGGTACGC
 14951 GGCCGCTCGA AGGCTGGCCG CGGGTATTGT CACTGTGCCC CCCAGGTCCA
 CCGGCGAGCT TCCGACCGGC GCCCATAACA GTGACACGGG GGGTCCAGGT
 15001 GGCGACGAGC GGCCGCGGCA GCAGCCGCGG CCATTAGTGC TATGACTCAG
 CCGCTGCTCG CCGGCGGCGT CGTCGGCGCC GGTAAATCAG ATACTGAGTC
 15051 GGTGCGAGGG GCAACGTGTA TTGGGTGCGC GACTCGGTTA GCGGCTGCG
 CCAGCGTCCC CGTTGCACAT AACCACGCG CTGAGCCAAT CGCCGACGC

Figure 27P

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15101 CGTGCCCGTG CCGCCCGCC CCCCAGCGCAA CTAGATTGCA AGAAAT
GCACGGGCAC GCGGGGCGG GGGGCGCGTT GATCTAACGT TCTTTT
15151 ACTTAGACTC GTACTGTTGT ATGTATCCAG CGGCGGCGGC GCGCAACGAA
TGAATCTGAG CATGACAACA TACATAGGTC GCCGCCGCCG CGCGTTGCTT
15201 GCTATGTCCA AGCGCAAAAT CAAAGAAGAG ATGCTCCAGG TCATCGCGCC
CGATACAGGT TCGCGTTTTA GTTCTCTCTC TACGAGGTCC AGTAGCGCGG
15251 GGAGATCTAT GGCCCCCGA AGAAGGAAGA GCAGGATTAC AAGCCCCGAA
CCTCTAGATA CCGGGGGGCT TCTTCCTTCT CGTCTAATG TTCGGGGCTT
15301 AGCTAAAGCG GGTCAAAAAG AAAAAGAAAG ATGATGATGA TGAACCTGAC
TCGATTTGCG CCAGTTTTC TTTTCTTTC TACTACTACT ACTTGAAGTG
15351 GACGAGGTGG AACTGCTGCA CGCTACCGCG CCCAGGCGAC GGGTACAGTG
CTGCTCCACC TTGACGACGT GCGATGGCGC GGGTCCGCTG CCCATGTCA
15401 GAAAGGTCGA CGCGTAAAAC GTGTTTTCG ACCCGGCACC ACCGTAGTCT
CTTCCAGCT GCGCATTTTG CACAAAACGC TGGGCCGTGG TGGCATCAGA
15451 TTACGCCCCG TGAGCGCTCC ACCCGCACCT ACAAGCGCGT GTATGATGAG
AATGCGGGCC ACTCGCGAGG TGGCGTGA TGTTCGCGCA CATACTACTC
15501 GTGTACGGCG ACGAGGACCT GCTTGAGCAG GCCAACGAGC GCCTCGGGGA
CACATGCCGC TGCTCTGGA CGAACTCGTC CGGTTGCTCG CGGAGCCCT
15551 GTTTCCTTAC GGAAAGCGGC ATAAGGACAT GCTGGCGTTG CCGCTGGACG
CAACGGATG CTTTTCGCG TATTCTGTG CGACCGCAAC GCGGACCTGC
15601 AGGGCAACCC AACACCTAGC CTAAGCCCG TAACACTGCA GCAGGTGCTG
TCCCGTTGGG TTGTGATCG GATTTCGGGC ATTGTGACGT CGTCCACGAC
15651 CCCGCGCTTG CACCGTCCGA AGAAAAGCGC GGCTTAAAGC GCGAGTCTGG
GGGCGCGAAC GTGGCAGGCT TCTTTTCGCG CCGGATTCG CGCTCAGACC
15701 TGACTTGGCA CCCACCGTGC AGCTGATGGT ACCCAAGCGC CAGCGACTGG
ACTGAACCGT GGGTGGCAGC TCGACTACCA TGGGTTGCGC GTCGCTGACC
15751 AAGATGTCTT GGAAAAATG ACCGTGGAAC CTGGGCTGGA GCCCGAGGTC
TTCTACAGAA CCTTTTTC TGGCACCTTC GACCCGACCT CGGGCTCCAG
15801 CGCGTGCGGC CAATCAAGCA GGTGGCGCCG GGAAGTGGCG TGCAGACCGT
GCGCACGCGG GTTAGTTCGT CCACCGCGGC CCGACCCGC ACGTCTGGCA
15851 GGACGTTTCA ATACCCACTA CCAAGTACAC CAGTATTGCC ACCGCCACAG
CCTGCAAGTC TATGGGTGAT GGTATCTGTC GTCATAACGG TGGCGGTGTC
15901 AGGGCATGGA GACACAAACG TCCCCGCTG CCTCAGCGGT GCGGATGCC
TCCGTACCT CTGTGTTTGC AGGGGCCAAC GGAGTCGCCA CCGCTACGG
15951 GCGGTGCAGG CGGTGCTGTC GGCGCGCTCC AAGACCTCTA CGGAGGTGCA
CGCCACGTCC GCCAGCGACG CCGGCGCAGG TTCTGGAGAT GCCTCCACGT
16001 AACGGACCCG TGGATGTTTC GCGTTTCAGC CCCCCGCGC CCGCGCGGTT
TTGCTGGGC ACCTACAAAG CGCAAAGTCG GGGGGCCGCG GCGCGGCAA

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Figure 27A

16051 CGAGGAAGTA CCGGCGCC AGCGCGCTAC TGCCCGAATA TGCCCTAAT
 GCTCCTTCAT GCCGCGGCGG TCGCGCGATG ACGGCTTAT ACGGGATGTA
 16101 CCTTCCATTG CGCCTACCCC CGGCTATCGT GGCTACACCT ACCGCCCCAG
 GGAAGGTAAC GCGGATGGGG GCCGATAGCA CCGATGTGGA TGGCGGGGTC
 16151 AAGACGAGCA ACTACCCGAC GCCGAACCAC CACTGGAACC CGCCGCCGCC
 TTCTGCTCGT TGATGGGCTG CGGCTTGGTG GTGACCTTGG GCGCGGCGCG
 16201 GTCGCCGTCG CCAGCCCGTG CTGGCCCCGA TTTCCGTGCG CAGGCTGGCT
 CAGCGGCAGC GGTGCGGCAC GACCGGGGCT AAAGGCACGC GTCCACCCGA
 16251 CGCGAAGGAG GCAGGACCCT GGTGCTGCCA ACAGCGCGCT ACCACCCAG
 GCGCTTCCTC CGTCTGGGA CCACGACGGT TGTCGCGCGA TGGTGGGGTC
 16301 CATCGTTTAA AAGCCGGTCT TTGTGGTTCT TGCAGATATG GCCCTCACCT
 GTAGCAAATT TTCGGCCAGA AACACCAAGA ACGTCTATAC CGGGAGTGGA
 16351 GCCGCTCCG TTTCCCGGTG CCGGGATTCC GAGGAAGAAT GCACCGTAGG
 CGGCGGAGGC AAAGGGCCAC GGCCCTAAGG CTCCTTCTTA CGTGGCATCC
 16401 AGGGGCATGG CCGGCCACGG CCTGACGGGC GGCATGCGTC GTGCGCACCA
 TCCCCGTACC GGCCGGTGCC GGA CTGCCCCG CCGTACGCAG CACCGTGGT
 16451 CCGCGGCGCG CGCGCGTCGC ACCGTGCGAT GCGCGGCGGT ATCCTGCCCC
 GGCCGCCGCC GCGCGCAGCG TGGCAGCGTA CCGCGCCCA TAGGACGGGG
 16501 TCCTTATTCC ACTGATCGCC GCGGCGATTG GCGCGGTGCC CGGAATTGCA
 AGGAATAAGG TGA CTAGCGG GCGCGCTAAC CCGGCGACGG GCCTTAACGT
 16551 TCCGTGGCCT TGCAGGCGCA GAGACACTGA TAAAAACAA GTTG CATGTG
 AGGCACCGGA ACGTCCGCGT CTCTGTGACT AATTTTGTG CAACGTACAC
 16601 GAAAAATCAA AATAAAAAGT CTGGACTCTC ACGCTCGCTT GGTCTGTAA
 CTTTTAGTT TTATTTTCA GACCTGAGAG TCGAGCGAA CCAGGACATT
 16651 CTATTTTGTA GAATGGAAGA CATCAACTTT GCGTCTCTGG CCGCGGACA
 GATAAACAT CTTACCTTCT GTAGTTGAAA CGCAGAGACC GGGGCGCTGT
 16701 CGGCTCGCGC CCGTTCATGG GAACTGGCA AGATATCGGC ACCAGCAATA
 GCCGAGCGCG GGCAAGTACC CTTTGACCGT TCTATAGCCG TGGTCGTAT
 16751 TGAGCGGTGG CGCCTTCAGC TGGGGCTCGC TGTGGAGCGG CATTAAAAAT
 ACTCGCCACC GCGGAAGTCG ACCCGAGCG ACACCTCGCC GTAATTTTAA
 16801 TTCGGTTCCA CCGTTAAGAA CTATGGCAGC AAGGCCTGGA ACAGCAGCAC
 AAGCCAAGGT GGCAATTCTT GATACCGTCG TTCCGGACCT TGTGTCGTG
 16851 AGGCCAGATG CTGAGGGATA AGTTGAAAGA GCAAAATTTC CAACAAAAGG
 TCCGGTCTAC GACTCCCTAT TCAACTTTCT CGTTTTAAAG GTTGTTTTCC
 16901 TGGTAGATGG CCTGGCCTCT GGCATTAGCG GGGTGGTGGG CCTGGCCAAC
 ACCATCTACC GGACCGGAGA CCGTAATCGC CCCACCACCT GGACCGGTG
 16951 CAGGCAGTGC AAAATAAGAT TAACAGTAAG CTGATCCCC GCCCTCCCGT
 GTCGTCACG TTTTATTCTA ATTGTCATTC GAACTAGGGG CGGGAGGGCA

Figure 27R

17001 AGAGGAGCCT CCGGCCG TGGAGACAGT GTCTCCAGAG GGGCGT
 TCTCCTCGGA GGTGGCCGCG ACCTCTGTCA CAGAGGTCTC CCCGCACCGC
 17051 AAAAGCGTCC GCGCCCCGAC AGGGAAGAAA CTCTGGTGAC GCAAATAGAC
 TTTTCGCAGG CGCGGGGCTG TCCCTTCTTT GAGACCACTG CGTTTATCTG
 17101 GAGCCTCCCT CGTACGAGGA GGCATAAAG CAAGGCCTGC CCACCACCCG
 CTCGGAGGGA GCATGCTCCT CCGTGATTTC GTTCCGGACG GGTGGTGGGC
 17151 TCCCATCGCG CCCATGGCTA CCGGAGTGCT GGGCCAGCAC ACACCCGTAA
 AGGGTAGCGC GGGTACCGAT GGCCTCACGA CCCGGTCTGT TGTGGGCATT
 17201 CGCTGGACCT GCCTCCCCC GCCGACACCC AGCAGAAACC TGTGCTGCCA
 GCGACCTGGA CGGAGGGGGG CGGCTGTGGG TCGTCTTTGG ACACGACGGT
 17251 GGGCCGACCG CCGTTGTTGT AACCCGTCTT AGCCGCGCGT CCTTGCGCCG
 CCGGGCTGGC GGCAACAACA TTGGGCAGGA TCGGCGCGCA GGGACCGCGC
 17301 CGCCGCCAGC GGTCCGCGAT CGTTGCGGCC CGTAGCCAGT GCAACTGGC
 GCGCGGTGCG CCAGGCGCTA GCAACGCCGG GCATCGGTCA CCGTTGACCG
 17351 AAAGCACACT GAACAGCATC GTGGGTCTGG GGGTGCAATC CCTGAAGCGC
 TTTCTGTGA CTGTCTGTAG CACCCAGACC CCCACGTTAG GGAATTGCGC
 17401 CGACGATGCT TCTGATAGCT AACGTGTCGT ATGTGTCTCA TGTATGCGTC
 GCTGCTACGA AGACTATCGA TTGCACAGCA TACACACAGT ACATACGCAG
 17451 CATGTCGCGC CCAGAGGAGC TGCTGAGCCG CCGCGCGCCC GCTTTCCAAG
 GTACAGCGGC GGTCTCCTCG ACGACTCGGC GCGCGCGGGG CGAAAGGTTT
 17501 ATGGCTACCC CTTCGATGAT GCCGCACTGG TCTTACATGC ACATCTCGGG
 TACCGATGGG GAAGCTACTA CGGCGTCACC AGAATGTACG TGTAGAGCCC
 17551 CCAGGACGCC TCGGAGTACC TGAGCCCCGG GCTGGTGACG TTTGCCCGCG
 GGTCTGCGG AGCCTCATGG ACTCGGGGCC CGACCACGTC AAACGGGCGC
 17601 CCACCGAGAC GTACTTCAGC CTGAATAACA AGTTTAGAAA CCCCACGGTG
 GGTGGCTCTG CATGAAGTCG GACTTATTGT TCAAATCTTT GGGGTGCCAC
 17651 CGCCTACGC ACCACGTGAC CACAGACCGG TCCAGCGTT TGACGCTGCG
 CGCGGATGCG TGCTGCACTG GTGTCTGGCC AGGGTCGCAA ACTCCGACCG
 17701 GTTCATCCCT GTGGACCGTG AGGATACTGC GTACTCGTAC AAGGCGCGGT
 CAAGTAGGGA CACCTGGCAC TCCTATGACG CATGAGCATG TTCCGCGCCA
 17751 TCACCCTAGC TGTGGGTGAT AACCGTGTGC TGGACATGGC TTCCACGTAC
 AGTGGGATCG ACACCCACTA TTGGCACACG ACCTGTACCG AAGGTGCATG
 17801 TTTGACATCC GCGGCGTGCT GGACAAGGGC CCTACTTTTA AGCCCTACTC
 AAAGTGTAGG CGCCGCACGA CCTGTCCCCG GGATGAAAAT TCGGGATGAG
 17851 TGGCACTGCC TACAACGCCC TGGCTCCCAA GGGTGCCCCA AATCCTTGCG
 ACCGTGACGG ATGTTGCGGG ACCGAGGGTT CCCACGGGGT TTAGGAACGC
 17901 AATGGGATGA AGCTGCTACT GCTCTTGAAA TAAACCTAGA AGAAGAGGAC
 TTACCCTACT TCGACGATGA CGAGAACTTT ATTTGGATCT TCTTCTCCTG

Figure 275

17951 GATGACAACG ACGAAGT AGACGAGCAA GCTGAGCAGC AAAAAA
CTACTGTTGC TTCTGCTTCA TCTGCTCGTT CGACTCGTCG TTTTGTGAGT

18001 CGTATTTGGG CAGGCGCCTT ATTCTGGTAT AAATATTACA AAGGAGGGTA
GCATAAACCC GTCCGCGGAA TAAGACCATA TTTATAATGT TTCCTCCCAT

18051 TTCAAATAGG TGTCGAAGGT CAAACACCTA AATATGCCGA TAAAACATTT
AAGTTTATCC ACAGCTTCCA GTTTGTGGAT TTATACGGCT ATTTTGTAAA

18101 CAACCTGAAC CTCAAATAGG AGAATCTCAG TGGTACGAAA CAGAAATTAA
GTTGGACTTG GAGTTTATCC TCTTAGAGTC ACCATGCTTT GTCTTTAATT

18151 TCATGCGAGCT GGGAGAGTCC TAAAAAAGAC TACCCCAATG AAACCATGTT
AGTACGTCGA CCCTCTCAGG ATTTTCTCTG ATGGGGTTAC TTTGGTACAA

18201 ACGGTTTCTA TGCAAAACCC ACAAATGAAA ATGGAGGGCA AGGCATTCTT
TGCCAAGTAT ACGTTTGGG TGTCTTACTT TACCTCCCGT TCCGTAAGAA

18251 GTAAAGCAAC AAAATGGAAA GCTAGAAAGT CAAGTGGAAG TGCAATTTTT
CATTTCTGTTG TTTTACCTTT CGATCTTTCA GTTCACCTTT ACGTTAAAAA

18301 CTCAACTACT GAGGCAGCCG CAGGCAATGG TGATAACTTG ACTCCTAAAG
GAGTTGATGA CTCCGTCGGC GTCCGTTACC ACTATTGAAC TGAGGATTTC

18351 TGGTATTGTA CAGTGAAGAT GTAGATATAG AAACCCAGAG CACTCATATT
ACCATAACAT GTCACCTTCA CATCTATATC TTTGGGGTCT GTGAGTATAA

18401 TCTTACATGC CCACTATTAA GGAAGGTAAC TCACGAGAAC TAATGGGCCA
AGAATGTACG GGTGATAATT CCTTCCATTG AGTGCTCTTG ATTACCCGGT

18451 ACAATCTATG CCCAACAGGC CTAATTACAT TGCTTTTAGG GACAATTTTA
TGTTAGATAC GGGTTGTCCG GATTAATGTA ACGAAAATCC CTGTTAAAAA

18501 TTGGTCTAAT GTATTACAAC AGCAGGGGTA ATATGGGTGT TCTGGCGGGC
AACCAGATTA CATAATGTTG TCGTGCCCAT TATACCCACA AGACCGCCCG

18551 CAAGCATCGC AGTTGAATGC TGTGTAGAT TTGCAAGACA GAAACACAGA
GTTGCTAGCG TCAACTTACG ACAACATCTA AACGTTCTGT CTTTGTGTCT

18601 GCTTTCATAC CAGCTTTTGC TTGATTCCAT TGGTGATAGA ACCAGGTACT
CGAAAGTATG GTCGAAAACG AACTAAGGTA ACCACTATCT TGGTCCATGA

18651 TTTCTATGTG GAATCAGGCT GTTGACAGCT ATGATCCAGA TGTTAGAATT
AAAGATACAC CTTAGTCCGA CAACTGTCGA TACTAGGTCT ACAATCTTAA

18701 ATTGAAAATC ATGGAAGTGA AGATGAAGTT CCAAATTACT GCTTTCCACT
TAACTTTTAG TACCTTGACT TCTACTTGAA GGTTTAATGA CGAAAGGTGA

18751 GGGAGGTGTG ATTAATACAG AGACTCTTAC CAAGGTAAAA CCTAAAACAG
CCCTCCACAC TAATTATGTC TCTGAGAATG GTTCCATTTT GGATTTTGTC

18801 GTCAGGAAAA TGGATGGGAA AAAGATGCTA CAGAATTTTC AGATAAAAAAT
CAGTCCTTTT ACCTACCCTT TTTCTACGAT GTCTTAAAAG TCTATTTTAA

18851 GAAATAAGAG TTGGAATAA TTTTGCCATG GAAATCAATC TAAATGCCAA
CTTTATTCTC AACCTTTATT AAAACGGTAC CTTTAGTTAG ATTTACGGTT

Figure 27T

18901 CCTGTGGAGA A TCCTGT ACTCCAACAT AGCGCTGTAT TTGCCC A
 GGACACCTCT TTAAAGGACA TGAGGTTGTA TCGCGACATA AACGGGCTGT
 18951 AGCTAAAGTA CAGTCCTTCC AACGTAAAAA TTTCTGATAA CCCAAACACC
 TCGATTTTCAT GTCAGGAAGG TTGCATTTT AAAGACTATT GGGTTTGTGG
 19001 TACGACTACA TGAACAAGCG AGTGGTGGCT CCCGGGCTAG TGGACTGCTA
 ATGCTGATGT ACTTGTTCGC TCACCACCGA GGGCCCGATC ACCTGACGAT
 19051 CATTAACCTT GGAGCACGCT GGTCCCTTGA CTATATGGAC AACGTCAACC
 GTAATTGGAA CCTCGTGCGA CCAGGGAAC TATATACCTG TTGCAGTTGG
 19101 CATTTAACCA CCACCGCAAT GCTGGCCTGC GCTACCGCTC AATGTTGCTG
 GTAAATTGGT GGTGGCGTTA CGACCGGACG CGATGGCGAG TTACAACGAC
 19151 GGCAATGGTC GCTATGTGCC CTTCCACATC CAGGTGCCTC AGAAGTTCTT
 CCGTTACCAG CGATACACGG GAAGGTGTAG GTCCACGGAG TCTTCAAGAA
 19201 TGCCATTA AAACCTCCTT TCCTGCCGGG CTCATACACC TACGAGTGGA
 ACGGTAATTT TTGGAGGAAG AGGACGGCCC GAGTATGTGG ATGCTCACCT
 19251 ACTTCAGGAA GGATGTTAAC ATGGTTCTGC AGAGCTCCCT AGGAAATGAC
 TGAAGTCCTT CCTACAATTG TACCAAGACG TCTCGAGGGA TCCTTTACTG
 19301 CTAAGGGTTG ACGGAGCCAG CATTAGTTT GATAGCATTT GCCTTTACGC
 GATTCCTAAC TGCTCGGTC GTAATTCAA CTATCGTAA CGGAAATGCG
 19351 CACCTTCTTC CCCATGGCCC ACAACACCGC CTCCACGCTT GAGGCCATGC
 GTGGAAGAAG GGGTACCGGG TGTGTGGCG GAGGTGCGAA CTCCGGTACG
 19401 TTAGAAACGA CACCAACGAC CAGTCCTTTA ACGACTATCT CTCCGCCGCC
 AATCTTTGCT GTGGTTGCTG GTCAGGAAAT TGCTGATAGA GAGGCGGCGG
 19451 AACATGCTCT ACCCTATACC CGCCAACGCT ACCAACGTGC CCATATCCAT
 TTGTACGAGA TGGGATATGG GCGGTTGCGA TGTTGTCACG GGTATAGGTA
 19501 CCCCTCCCGC AACTGGGCGG CTTTCCGCGG CTGGGCTTTC ACGCGCCTTA
 GGGGAGGGCG TTGACCCGCC GAAAGGCGCC GACCCGGAAG TCGCGGGAAT
 19551 AGACTAAGGA AACCCCATCA CTGGGCTCGG GCTACGACCC TTATTACACC
 TCTGATTCCT TTGGGGTAGT GACCCGAGCC CGATGCTGGG AATAATGTGG
 19601 TACTCTGGCT CTATACCCTA CCTAGATGGA ACCTTTTACC TCAACCACAC
 ATGAGACCGA GATATGGGAT GGATCTACCT TGGAAAATGG AGTTGGTGTG
 19651 CTTTAAGAAG GTGGCCATTA CCTTTGACTC TTCTGTCAGC TGGCCTGGCA
 GAAATTCCTT CACCGGTAAT GGAACTGAG AAGACAGTCG ACCGGACCGT
 19701 ATGACCGCCT GCTTACCCCC AACGAGTTTG AAATTAAGCG CTCAGTTGAC
 TACTGGCGGA CGAATGGGGG TTGCTCAAAC TTTAATTCGC GAGTCAACTG
 19751 GGGGAGGGTT ACAACGTTGC CCACTGTAAC ATGACCAAAG ACTGGTTCTT
 CCCCTCCCAA TGTGCAACG GTCACATTG TACTGGTTTC TGACCAAGGA
 19801 GGTACAAATG CTAGCTAACT ATAACATTGG CTACCAGGCG TTCTATATCC
 CCATGTTTAC GATCGATTGA TATTGTAACC GATGGTCCCG AAGATATAGG

Figure 274

19851 CAGAGAGCTA C GACCGC ATGTACTCCT TCTTTAGAAA CTTCCA
GTCTCTCGAT GTTCTGCGG TACATGAGGA AGAAATCTTT GAAGGTCGGG

19901 ATGAGCCGTC AGGTGGTGA TGATACTAAA TACAAGGACT ACCAACAGGT
TACTCGGCAG TCCACCACCT ACTATGATTT ATGTTCTCTGA TGGTTGTCCA

19951 GGGCATCCTA CACCAACACA ACAACTCTGG ATTTGTTGGC TACCTTGCCC
CCCGTAGGAT GTGGTTGTGT TGTGAGACC TAAACAACCG ATGGAACGGG

20001 CCACCATGCG CGAAGGACAG GCCTACCCTG CTAACCTCCC CTATCCGCTT
GGTGGTACGC GCTTCTGTG CCGATGGGAC GATTGAAGGG GATAGCGGAA

20051 ATAGGCAAGA CCGCAGTTGA CAGCATTACC CAGAAAAAGT TTCTTTGCGA
TATCCGTTCT GCGCTCAACT GTCGTAATGG GTCTTTTCA AAGAAACGCT

20101 TCGCACCCCTT TGGCGCATCC CATTCTCCAG TAACTTTATG TCCATGGGCG
AGCGTGGGAA ACCGCTAGG GTAAGAGGTC ATTGAAATAC AGGTACCCCG

20151 CACTCACAGA CCTGGGCCAA AACCTTCTCT ACGCCAATC CGCCACGCG
GTGAGTGTCT GGACCCGTT TTGGAAGAGA TCGGTTGAG GCGGGTGC

20201 CTAGACATGA CTTTGTAGGT GGATCCCATG GACGAGCCCA CCCTTCTTTA
GATCTGTACT GAAACTCCA CCTAGGGTAC CTGCTCGGGT GGAAGAAAT

20251 TGTTTTGT TT GAAGTCTTTG ACGTGGTCCG TGTGCACCAG CCGCACCGCG
ACAAAACAAA CTTAGAAAC TGCACCAGGC ACACGTGGTC GCGGTGGCG

20301 GCGTCATCGA AACCCTGTAC CTGCGCACGC CTTCTCGGC CGGCAACGCC
CGCAGTAGCT TTGGCATATG GACGCGTGGC GGAAGAGCCG GCCGTGCGG

20351 ACAACATAAA GAAGCAAGCA ACATCAACAA CAGCTGCCGC CATGGGCTCC
TGTGTATTT CTTCTGTTCT TGTAGTTGTT GTCGACGGCG GTACCCGAGG

20401 AGTGAGCAGG AACTGAAAGC CATTGTCAA GATCTTGTT GTGGGCCATA
TCACTCGTCC TTGACTTTG GTAACAGTT CTAGAACCA CACCCGGTAT

20451 TTTTTTGGGC ACCTATGACA AGCGCTTTCC AGGCTTTGTT TCTCCACACA
AAAAAACCCG TGGATACTGT TCGCGAAAGG TCCGAAACAA AGAGGTGTGT

20501 AGCTCGCCTG CGCCATAGTC AATACGCGCG GTCGCGAGAC TGGGGCGTA
TCGAGCCGAC GCGGTATCAG TTATGCCGCG CAGCGCTCTG ACCCCGCGAT

20551 CACTGGATGG CTTTGCCTG GAACCCGCAC TCAAAAACAT GCTACCTCTT
GTGACCTACC GGAAACGGAC CTTGGGCGTG AGTTTTTGTA CGATGGAGAA

20601 TGAGCCCTTT GGCTTTTCTG ACCAGCGACT CAAGCAGGTT TACCAGTTTG
ACTCGGGAAA CCGAAAAGAC TGGTCGCTGA GTTCGTCCAA ATGGTCAAAC

20651 AGTACGAGTC ACTCTGCGC CGTAGCGCCA TTGCTTCTTC CCCCACCGC
TCATGCTCAG TGAGGACGCG GCATCGCGGT AACGAAGAAG GGGGCTGGCG

20701 TGTATAACGC TGGAAAAGTC CACCCAAAGC GTACAGGGGC CCAACTCGGC
ACATATTGCG ACCTTTTCAG GTGGGTTTCT CATGTCCCCG GGTGAGCCG

20751 CGCCTGTGGA CTATTCTGCT GCATGTTTCT CCACGCCTTT GCCAACTGGC
GCGGACACCT GATAAGACGA CGTACAAAGA GGTGCGGAAA CGGTTGACCG

Figure 27 V.

20801 CCCAAACTCC C GATCAC AACCCACCA TGAACCTTAT TACCGG A
 GGGTTTGAGG GTACCTAGTG TTGGGGTGGT ACTTGGAATA ATGGCCCCAT
 20851 CCCAACTCCA TGCTCAACAG TCCCCAGGTA CAGCCACCC TGCGTCGCAA
 GGGTTGAGGT ACGAGTTGTC AGGGGTCCAT GTCGGGTGGG ACGCAGCGTT
 20901 CCAGGAACAG CTCTACAGCT TCCTGGAGCG CCACTCGCCC TACTTCCGCA
 GGTCCTTGTC GAGATGTCGA AGGACCTCGC GGTGAGCGGG ATGAAGCGCT
 20951 GCCACAGTGC GCAGATTAGG AGCGCCACTT CTTTTGTCA CTTGAAAAAC
 CCGTGTCACG CGTCTAATCC TCGCGGTGAA GAAAAACAGT GAACTTTTTG
 21001 ATGTAAAAAT AATGTACTAG AGACACTTTC AATAAAGGCA AATGCTTTTA
 TACATTTTTA TTACATGATC TCTGTGAAAG TTATTTCCTT TTACGAAAAAT
 21051 TTTGTACACT CTCGGGTGAT TATTTACCCC CACCCTTGCC GTCTGCGCCG
 AAACATGTGA GAGCCCACTA ATAAATGGGG GTGGGAACGG CAGACGCGGC
 21101 TTTAAAAATC AAAGGGGTTT TGCCGCGCAT CGCTATGCGC CACTGGCAGG
 AAATTTTTAG TTTCCCAAG ACGGCGCGTA GCGATACGCG GTGACCGTCC
 21151 GACACGTTGC GATACTGGTG TTTAGTGCTC CACTTAAACT CAGGCACAAC
 CTGTGCAACG CTATGACCAC AAATCAGGAG GTGAATTGTA GTCCGTGTTG
 21201 CATCCGCGGC AGCTCGGTGA AGTTTTCACT CCACAGGCTG CGCACCATCA
 GTAGGCGCCG TCGAGCCACT TCAAAAGTGA GGTGTCCGAC GCGTGGTAGT
 21251 CCAACGCGTT TAGCAGGTCG GCGCCCGATA TCTTGAAATC GCAGTTGGGG
 GGTGCGCAA ATCGTCCAGC CCGCGGCTAT AGAATTCAG CGTCAACCCC
 21301 CCTCCGCCCT GCGCGCGCGA GTTGCATAC ACAGGGTTGC AGCACTGGAA
 GGAGCGGGA CGCGCGCGCT CAACGCTATG TGTCCCAACG TCGTGACCTT
 21351 CACTATCAGC GCCGGGTGGT GCACGCTGGC CAGCAGGCTC TTGTGCGAGA
 GTGATAGTCG CGGCCACCA CGTGCGACCG GTCGTGCGAG AACAGCCTCT
 21401 TCAGATCCGC GTCCAGGTCC TCCGCGTTGC TCAGGGCGAA CGGAGTCAAC
 AGTCTAGGCG CAGGTCCAGG AGGCGCAACG AGTCCCGCTT GCCTCAGTTG
 21451 TTTGGTAGCT GCCTTCCCAA AAAGGGCGCG TGCCAGGCT TTGAGTTGCA
 AAACCATCGA CGGAAGGGT TTTCCGCGC ACGGGTCCGA AACTCAACGT
 21501 CTCGCACCST AGTGGCATCA AAAGGTGACC GTGCCCGGTC TGGGCGTTAG
 GAGCGTGGCA TCACCGTAGT TTTCCACTGG CACGGGCCAG ACCCGCAATC
 21551 GATACAGCGC CTGCATAAAA GCCTTGATCT GCTTAAAAGC CACCTGAGCC
 CTATGTCGCG GACGTATTTT CGGAAC TAGA CGAATTTTCG GTGGACTCGG
 21601 TTTGCGCCTT CAGAGAAGAA CATGCCGCAA GACTTGCCGG AAAACTGATT
 AAACGCGGAA GTCTCTTCTT GTACGGCGTT CTGAACGGCC TTTTGACTAA
 21651 GGCCGGACAG GCCGCGTCGT GCACGCAGCA CTTGCGTCG GTGTGGAGA
 CCGGCTGTC CGGCGCAGCA CGTGCGTCGT GGAACGCAGC CACAACCTCT
 21701 TCTGCACCAC ATTTTCGGCC CACCGGTTCT TCACGATCTT GGCCTTGCTA
 AGACGTGGTG TAAAGCCGGG GTGGCCAAGA AGTGCTAGAA CCGGAACGAT

Figure 27W

21751 GACTGCTCCT TCGCGCG CTGCCCGTTT TCGCTCGTCA CATCCAT
CTGACGAGGA AGTCGCGCGC GACGGGCAAA AGCGAGCAGT GTAGGTAAAG

21801 AATCACGTGC TCCTTATTTA TCATAATGCT TCCGTGTAGA CACTTAAGCT
TTAGTGCACG AGGAATAAAT AGTATTACGA AGGCACATCT GTGAATTCTGA

21851 CGCCTTCGAT CTCAGCGCAG CGGTGCAGCC ACAACGCGCA GCCCGTGGGC
CGGGAAGCTA GAGTCGCGTC GCCACGTCGG TGTTCGCGCT CGGGCACCCG

21901 TCGTGATGCT TGTAGGTCAC CTCTGCAAAC GACTGCAGGT ACGCCTGCAG
AGCACTACGA ACATCCAGTG GAGACGTTTG CTGACGTCCA TGCGGACGTC

21951 GAATCGCCCC ATCATCGTCA CAAAGGTCTT GTTGCTGGTG AAGGTCAGCT
CTTAGCGGGG TAGTAGCAGT GTTTCAGAA CAACGACCAC TTCCAGTCGA

22001 GCAACCCGCG GTGCTCCTCG TTCAGCCAGG TCTTGCATAC GGCCGCCAGA
CGTTGGGCGC CACGAGGAGC AAGTCGGTCC AGAACGTATG CCGCGCGTCT

22051 GCTTCCACTT GGTGAGGCG TAGTTTGAAG TTCGCCTTTA GATCGTTATC
CGAAGGTGAA CCACTCCGTC ATCAAACTTC AAGCGGAAAT CTAGCAATAG

22101 CACGTGGTAC TTGTCCATCA GCGCGCGCGC AGCCTCCATG CCCTTCTCCC
GTGACCATG AACAGGTAGT CGCGCGCGCG TCGGAGGTAC GGAAGAGGG

22151 ACGCAGACAC GATCGGCACA CTCAGCGGGT TCATCACCGT AATTTCACTT
TGCCTCTGTG CTAGCCGTGT GAGTCGCCCA AGTAGTGGCA TTAAAGTGAA

22201 TCCGCTTCGC TGGGCTCTTC CTCTTCTCT TCGCTCCGCA TACCACGCGC
AGGCGAAGCG ACCCGAGAAG GAGAAGGAGA ACGCAGGCGT ATGGTTCGCG

22251 CACTGGGTGC TCTTCATTCA GCCGCCGCAC TGTGCGCTTA CCTCCTTTGC
GTGACCCAGC AGAAGTAAGT CGGCGGCGTG ACACGCGAAT GGAGGAAACG

22301 CATGCTTGAT TAGCACCGET GGTTTGCTGA AACCACCAT TTGTAGCGCC
GTACGAACTA ATCGTGGCCA CCAACGACT TTGGGTGGTA AACATCGCGG

22351 ACATCTTCTC TTTCTTCTC GCTGTCCACG ATTACCTCTG GTGATGGCGG
TGTAAGAGAG AAAGAAGGAG CGACAGGTGC TAATGGAGAC CACTACCGCC

22401 GCGCTCGGGC TTGGGAGAAG GCGCTTCTT TTTCTTCTTG GCGCAATGG
CGCGAGCCCG AACCTCTTC CCGCAAGAA AAAGAAGAAC CCGCGTTACC

22451 CCAAATCCGC CGCCGAGGTC GATGGCCGCG GGCTGGGTGT GCGCGGCACC
GGTTTAGGCG GCGGCTCCAG CTACCGGCGC CCGACCCACA CGCGCCGTGG

22501 AGCGCGTCTT GTGATGAGTC TTCCTCGTCC TCGGACTCGA TACGCCGCTT
TCGCGCAGAA CACTACTCAG AAGGAGCAGG AGCCTGAGCT ATGCGGCGGA

22551 CATCCGCTTT TTTGGGGGCG CCCGGGGAGG CGGCGGCGAC GGGGACGGGG
GTAGGGGAAA AAACCCCGC GGGCCCTCC GCGCGCGTG CCCCTGCCCC

22601 ACGACACGTC CTCCATGGTT GGGGACGTC GCGCCGCACC GCGTCCGCGC
TGCTGTGCAG GAGGTACCAA CCCCTGCAG CGCGGCGTGG CGCAGGCGCG

22651 TCGGGGGTGG TTTGCGGCTG CTCTCTTCC CGACTGGCCA TTTCTTCTC
AGCCCCACC AAAGCGCGAC GAGGAGAAGG GCTGACCGGT AAAGGAAGAG

Figure 27X

22701 CTATAGGCAG AAGATCA TGGAGTCAGT CGAGAAGAAG GACAGC
GATATCCGTC TTTTCTAGT ACCTCAGTCA GCTCTTCTTC CTGTCCGATT

22751 CCGCCCCCTC TGAGTTCGCC ACCACCGCCT CCACCGATGC CGCCAACGCG
GGCGGGGGAG ACTCAAGCGG TGGTGGCGGA GGTGGCTACG GCGGTTGCGC

22801 CCTACCACCT TCCCCGTCGA GGCACCCCGC CTTGAGGAGG AGGAAGTGAT
GGATGGTGGA AGGGGCAGCT CCGTGGGGGC GAACTCCTCC TCCTTCACTA

22851 TATCGAGCAG GACCCAGGTT TTGTAAGCGA AGACGACGAG GACCGCTCAG
ATAGCTCGTC CTGGGTCCAA AACATTGCT TCTGCTGCTC CTGGCGAGTC

22901 TACCAACAGA GGATAAAAAG CAAGACCAGG ACAACGCAGA GGCAACGAG
ATGTTGTCTT CCTATTTTTC GTTCTGGTCC TGTGCGTCT CCGTTTGCTC

22951 GAACAAGTCG GCGGGGGGA CGAAGGCAT GCGGACTACC TAGATGTGGG
CTTGTTCAGC CCGCCCCCT GCTTCCGTA CCGCTGATGG ATCTACACCC

23001 AGACGACGTG CTGTGAAGC ATCTGCAGCG CCAGTGCGCC ATTATCTGCG
TCTGCTGCAC GACAACTTCG TAGACGTCGC GGTACGCGG TAATAGACGC

23051 ACGCGTTGCA AGAGCGCAGC GATGTGCCCC TCGCCATAGC GGATGTCAGC
TGCGCAACGT TCTCGCGTCG CTACACGGGG AGCGGTATCG CCTACAGTCG

23101 CTTGCCTACG AACGCCACCT ATTCTCACCG CGCGTACCCC CCAAACGCCA
GAACGGATGC TTGCGGTGGA TAAGAGTGGC GCGCATGGGG GGTTTGCGGT

23151 AGAAAACGGC ACATGCGAGC CCAACCCGCG CCTCAACTTC TACCCCGTAT
TCTTTTGCCG TGTACGCTCG GGTGGGCGC GGAGTTGAAG ATGGGGCATA

23201 TTGCCGTGCC AGAGGTGCTT GCCACCTATC ACATCTTTT CCAAACTGC
AACGGCACGG TCTCCACGAA CGGTGGATAG TGTAGAAAAA GGTTTGACG

23251 AAGATACCCC TATCTGCCC TGCCAACCGC AGCCGAGCGG ACAAGCAGCT
TTCTATGGGG ATAGGACGGC ACGGTTGGCG TCGGCTCGCC TGTTCGTCGA

23301 GGCTTGCGG CAGGGCGCTG TCATACCTGA TATCGCCTCG CTCAACGAAG
CCGGAACGCC GTCCCGCGAC AGTATGGACT ATAGCGGAGC GAGTTGCTTC

23351 TGCCAAAAAT CTTTGAGGGT CTTGGACGCG ACGAGAAGCG CGCGGCAAC
ACGGTTTTTA GAAACTCCCA GAACCTGCGC TGCTCTTCGC GCGCCGTTG

23401 GCTCTGCAAC AGGAAAACAG CGAAAATGAA AGTCACTCTG GAGTGTGGT
CGAGACGTTG TCCTTTTGTC GCTTTACTT TCAGTGAGAC CTCACAACCA

23451 GGAACTCGAG GGTGACAACG CGCGCCTAGC CGTACTAAAA CGCAGCATCG
CCTTGAGCTC CCACTGTTGC GCGCGGATCG GCATGATTTT GCGTCGTAGC

23501 AGGTCACCCA CTTTGCTTAC CCGGCACTTA ACCTACCCCC CAAGGTCATG
TCCAGTGGGT GAAACGGATG GGCCGTGAAT TGGATGGGG GTTCCAGTAC

23551 AGCACAGTCA TGAGTGAGCT GATCGTGCGC CGTGCGCAGC CCCTGGAGAG
TCGTGTCACT ACTCACTCGA CTAGCACGCG GCACGCGTCG GGGACCTCTC

23601 GGATGCAAAAT TTGCAAGAAC AAACAGAGGA GGGCCTACCC GCAGTTGGCG
CCTACGTTTA AACGTTCTTG TTTGTCTCCT CCCGGATGGG CGTCAACCGC

Figure 27 Y

23651 ACGAGCAGCT ACGCTGG CTTCAAACGC GCGAGCCTGC CCACTT G
TGCTCGTCGA TCGCGCGACC GAAGTTTGGC CGCTCGGACG GCTGAACCTC

23701 GAGCGACGCA AACTAATGAT GGCCGCAGTG CTCGTTACCG TGGAGCTTGA
CTCGCTGCGT TTGATTACTA CCGGCGTCAC GAGCAATGGC ACCTCGAAT

23751 GTGCATGCAG CGGTCTTTG CTGACCCGGA GATGCAGCGC AAGCTAGAGG
CACGTACGTC GCCAAGAAAC GACTGGGCCT CTACGTCGCG TTCGATCTCC

23801 AAACATTGCA CTACACCTTT CGACAGGGCT ACGTACGCCA GGCCTGCAAG
TTTGTAAAGT GATGTGAAA GCTGTCCCGA TGCATGCGGT CCGGACGTTT

23851 ATCTCCAACG TGGAGCTCTG CAACCTGGTC TCCTACCTTG GAATTTTGCA
TAGAGGTTGC ACCTCGAGAC GTTGGACCAG AGGATGGAAC CTTAAAACGT

23901 CGAAAACCGC CTTGGGCAAA ACGTGCTTCA TTCCACGCTC AAGGGCGAGG
GCTTTTGGCG GAACCCGTTT TGCACGAAGT AAGGTGCGAG TTCCCGCTCC

23951 CGCGCCGCGA CTACGTCCGC GACTGCGTTT ACTTATTTCT ATGCTACACC
GCGCGGCGCT GATGCAGGCG CTGACGCAAA TGAATAAAGA TACGATGTGG

24001 TGGCAGACGG CCATGGGCGT TTGGCAGCAG TGCTTGGAGG AGTGCAACCT
ACCGTCTGCC GGTACCCGCA AACCGTCGTC ACGAACCTCC TCACGTTGGA

24051 CAAGGAGCTG CAGAACTGC TAAAGCAAAA CTTGAAGGAC CTATGGACGG
GTTCTCTGAC GTCTTTGACG ATTTCGTTTT GAACTTCCTG GATACCTGCC

24101 CTTTCAACGA GCGCTCCGTG GCCGCGCACG TGGCGGACAT CATTTTCCCC
GGAAGTTGCT CCGGAGGCAC CGGCGCGTGG ACCGCCTGTA GTAAAAGGGG

24151 GAACGCCTGC TTAACCCCT GCAACAGGGT CTGCCAGACT TCACCAGTCA
CTTGCGGACG AATTTTGGGA CGTTGTCCCA GACGGTCTGA AGTGGTCAGT

24201 AAGCATGTTG CAGAACTTTA GGAACCTTAT CCTAGAGCGC TCAGGAATCT
TTCGTACAAC GTCTTGAAAT CCTTGAAATA GGATCTCGCG AGTCCTTAGA

24251 TGCCCGCCAC CTGCTGTGCA CTTCTAGCG ACTTTGTGCC CATTAAGTAC
ACGGGCGGTG GACGACACGT GAAGGATCGC TGAAACACGG GTAATTCATG

24301 CGCGAATGCC CTCCGCCGCT TTGGGGCCAC TGCTACCTTC TGCAGCTAGC
GCGCTTACGG GAGGCGGCGA AACCCCGGTG ACGATGGAAG ACGTCGATCG

24351 CAACTACCTT GCCTACCACT CTGACATAAT GGAAGACGTG AGCGGTGACG
GTTGATGGAA CGGATGGTGA GACTGTATTA CTTCTGCAC TCGCCACTGC

24401 GTCTACTGGA GTGTCACTGT CGCTGCAACC TATGCACCCC GCACCGCTCC
CAGATGACCT CACAGTGACA GCGACGTTGG ATACGTGGGG CGTGGCGAGG

24451 CTGGTTTGCA ATTCGCAGCT GCTTAACGAA AGTCAAATTA TCGGTACCTT
GACCAAACGT TAAGCGTCGA CGAATTGCTT TCAGTTTAAT AGCCATGGAA

24501 TGAGCTGCAG GGTCCCTCGC CTGACGAAAA GTCCGCGGCT CCGGGGTGA
ACTCGACGTC CCAGGGAGCG GACTGCTTTT CAGGCGCCGA GGCCCCAACT

24551 AACTCACTCC GGGGCTGTGG ACGTCGGCTT ACCTTCGCAA ATTTGTACCT
TTGAGTGAGG CCCCGACACC TGCAGCCGAA TGGAAGCGTT TAAACATGGA

Figure 27 Z

24601 GAGGACTACC A~~CT~~CCACGA GATTAGGTTT TACGAAGACC AATCCCC~~CC~~
 CTCTGTATGG TCGGGGTGCT CTAATCCAAG ATGCTTCTGG TTAGGGCGGG
 24651 GCCTAATGCG GAGCTTACCG CTGCGTCAT TACCCAGGGC CACATTCTTG
 CGGATTACGC CTCGAATGGC GGACGCAGTA ATGGGTCCCG GTGTAAGAAC
 24701 GCCAATTGCA AGCCATCAAC AAAGCCCGCC AAGAGTTTCT GCTACGAAAG
 CGGTTAACGT TCGGTAGTTG TTTCGGGCGG TTCTCAAAGA CGATGCTTTC
 24751 GGACGGGGGG TTTACTTGGA CCCCAGTCC GCGAGGAGC TCAACCCAAT
 CCTGCCCCC AAATGAACCT GGGGGTCAGG CCGCTCCTCG AGTTGGGTTA
 24801 CCCCCGCGC CCGCAGCCCT ATCAGCAGCA GCCCGGGCC CTGCTTCCC
 GGGGGGCGC GCGTCGGGA TAGTCGTCGT CGGCGCCCGG GAACGAAGGG
 24851 AGGATGGCAC CCAAAAAGAA GCTGCAGCTG CCGCCGCCAC CCACGGACGA
 TCCTACCGTG GGT~~TTTT~~CTT CGACGTCGAC GGCGGCGGTG GTGCTCTCT
 24901 GGAGGAATAC TGGGACAGTC AGGCAGAGGA GGT~~TTTT~~TGGAC GAGGAGGAGG
 CCTCCTATG ACCCTGTCAG TCCGTCTCCT CCAAAACCTG CTCCTCCTCC
 24951 AGGACATGAT GGAAGACTGG GAGAGCCTAG ACGAGGAAGC TTCCGAGGTC
 TCCTGTACTA CCTTCTGACC CTCTCGGATC TGCTCCTTCG AAGGCTCCAG
 25001 GAAGAGGTGT CAGACGAAAC ACCGTCACCC TCGGTGCGAT TCCCCTCGCC
 CTCTCCACA GTCTGCTTTG TGGCAGTGGG AGCCAGCGTA AGGGGAGCGG
 25051 GGCGCCCCAG AAATCGGCAA CCGGTTCAG CATGGCTACA ACCTCCGCTC
 CCGCGGGGTC TTTAGCCGTT GGCCAAGGTC GTACCGATGT TGGAGGCGAG
 25101 CTCAGGCGCC GCCGGCACTG CCCGTTCCGC GACCCAACCG TAGATGGGAC
 GAGTCCGCGG CGGCCGTGAC GGGCAAGCGG CTGGGTGGC ATCTACCTGC
 25151 ACCACTGGAA CCAGGGCCGG TAAGTCCAAG CAGCCGCCGC CGTTAGCCCA
 TGGTGACCTT GGTCCCAGCC ATTCAGGTTT GTCGGCGGCG GCAATCGGGT
 25201 AGAGCAACAA CAGCGCCAAG GCTACCGCTC ATGGCGCGGG CACAAGAACG
 TCTCGTTGTT GTCGCGGTTT CGATGGCGAG TACCGCGCCC GTGTTCTTGC
 25251 CCATAGTTGC TTGCTTGCAA GACTGTGGGG GCAACATCTC CTTCGCCCGC
 GGTATCAACG AACGAACGTT CTGACACCCC CTTGTAGAG GAAGCGGGCG
 25301 CGCTTTCTTC TCTACCATCA CGGCGTGGCC TTCCCCCGTA ACATCCTGCA
 GCGAAAGAAG AGATGGTAGT GCCGCACCGG AAGGGGGCAT TGTAGGACGT
 25351 TTTACTACCGT CATCTCTACA GCCATACTG CACCGCGGGC AGCGGCAGCA
 AATGATGGCA GTAGAGATGT CGGGTATGAC GTGGCCGCGG TCGCCGTCGT
 25401 ACAGCAGCGG CCACACAGAA GCAAAGGCGA CCGGATAGCA AGACTCTGAC
 TGTGTCGCGC GGTGTGTCTT CGTTTCCGCT GGCCTATCGT TCTGAGACTG
 25451 AAAGCCCAAG AAATCCACAG CGCGCGCAGC AGCAGGAGGA GGAGCGCTGC
 TTTCGGGTTT TTTAGGTGTC GCCGCCGTCG TCGTCTCCTT CCTCGCGACG
 25501 GTCTGGCGCC CAACGAACCC GTATCGACCC GCGAGCTTAG AAACAGGATT
 CAGACCGCGG GTTGCTTGGG CATAGCTGGG CGCTCGAATC TTTGTCTTAA

Figure 27 AA

25551 TTCCCCACTC TCTTGCTAT ATTTCAACAG AGCAGGGGCC AAGAACA
 AAAGGGTGAG ACATACGATA TAAAGTGTGTC TCGTCCCCGG TTCTTGTTCT

25601 GCTGAAAATA AAAAACAGGT CTCTGCGATC CCTCACCCGC AGCTGCCTGT
 CGACTTTTAT TTTTGTCCA GAGACGCTAG GGAGTGGGCG TCGACGGACA

25651 ATCACA AAAAG CGAAGATCAG CTTCGGCGCA CGCTGGAAGA CGCGGAGGCT
 TAGTGT TTTTC GCTTCTAGTC GAAGCCGCGT GCGACCTTCT GCGCCTCCGA

25701 CTCTTCAGTA AATACTGCGC GCTGACTCTT AAGGACTAGT TTCGCGCCCT
 GAGAAGTCAT TTATGACGCG CGACTGAGAA TTCTTGATCA AAGCGCGGGA

25751 TTCTCAAATT TAAGCGCGAA AACTACGTCA TCTCCAGCGG CCACACCCGG
 AAGAGTTTAA ATTCGCGCTT TTGATGCAGT AGAGGTGCGC GGTGTGGGCC

25801 CGCCAGCACC TGTGTGTCAGC GCCATTATGA GCAAGGAAAT TCCCACGCCC
 GCGGTGCTGG ACAACAGTCG CGGTAATACT CGTTCTTTTA AGGGTGCGGG

25851 TACATGTGGA GTTACCAGCC ACAAAATGGGA CTTGCGGCTG GAGCTGCCCC
 ATGTACACCT CAATGGTTCG TGTTTACCTT GAACGCCGAC CTCGACGGGT

25901 AGACTACTCA ACCCGAATAA ACTACATGAG CGCGGGACCC CACATGATAT
 TCTGATGAGT TGGGCTTATT TGATGTACTC GCGCCCTGGG GTGTACTATA

25951 CCCGGGTCAA CGGAATACGC GCCCACCGAA ACCGAATTCT CCTGGAACAG
 GGGCCCACTT GCCTTATGCG CGGGTGGCTT TGGCTTAAGA GGACCTTGTC

26001 GCGGCTATTA CCACCACACC TCGTAATAAC CTTAATCCCC GTAGTTGGCC
 CGCCGATAAT GGTGGTGTGG AGCATTATTG GAATTAGGGG CATCAACCGG

26051 CGCTGCCCTG GTGTACCAGG AAAGTCCCGC TCCCACCACT GTGGTACTTC
 GCGACGGGAC CACATGGTCC TTTCAGGGCG AGGGTGGTGA CACCATGAAG

26101 CCAGAGACGC CCAGGCCGAA GTTCAGATGA CTAACTCAGG GCGCGAGCTT
 GGTCTCTGCG GGTCCGGCTT CAAGTCTACT GATTGAGTCC CCGCGTCGAA

26151 GCGGGCGGCT TTCGTACAG GGTGCGGTGCG CCCGGGCAGG GTATAACTCA
 CGCCGCCGA AAGCAGTGTG CCACGCCAGC GGGCCCGTCC CATATTGAGT

26201 CCTGACAATC AGAGGGCGAG GTATTACGCT CAACGACGAG TCGGTGAGCT
 GGACTGTTAG TCTCCCGCTC CATAAGTCGA GTTGCTGCTC AGCCACTCGA

26251 CCTCGCTTGG TCTCCGTCCG GACGGGACAT TTCAGATCGG CGGCGCCGGC
 GGAGCGAACC AGAGGCAGGC CTGCCCTGTA AAGTCTAGCC GCCGCGGCCG

26301 CGCTCTTCAT TCACGCCTCG TCAGGCAATC CTAACCTGTC AGACCTCGTC
 GCGAGAAGTA AGTGCGGAGC AGTCCGTTAG GATTGAGACG TCTGGAGCAG

26351 CTCTGAGCCG CGCTCTGGAG GCATTGGAAC TCTGCAATTT ATTGAGGAGT
 GAGACTCGGC GCGAGACCTC CGTAACCTTG AGACGTTAAA TAACTCCTCA

26401 TTGTGCCATC GGTCTACTTT AACCCCTTCT CGGGACCTCC CGGCCACTAT
 AACACGGTAG CCAGATGAAA TTGGGGAAGA GCCCTGGAGG GCCGGTGATA

26451 CCGGATCAAT TTATTCCTAA CTTTGACGCG GTAAAGGACT CGGCGGACGG
 GGCCTAGTTA AATAAGGATT GAAACTGCGC CATTTCTGTA GCCGCCTGCC

Figure 27 AB

26501 CTACGACTGA A TAAGTG GAGAGGCAGA GCAACTGCCG CTGAAA C
 GATGCTGACT TACAATTAC CTCCTCGTCT CGTTGACGCG GACTTTGTGG
 26551 TGGTCCACTG TCGCCGCCAC AAGTGCTTTG CCCGCGACTC CGGTGAGTTT
 ACCAGGTGAC AGCGCGCGTG TTCACGAAAC GGGCGCTGAG GCCACTCAAA
 26601 TGCTACTTTG AATTGCCCCG GGATCATATC GAGGGCCCCG CGCACGGCGT
 ACGATGAAAC TTAACGGGCT CCTAGTATAG CTCCTGGGCC GCGTGCCGCA
 26651 CCGGCTTACC GCCCAGGGAG AGCTTGCCCG TAGCCTGATT CGGGAGTTTA
 GGCCGAATGG CGGCTCCCTC TCGAACGGGC ATCGGACTAA GCCCTCAAAT
 26701 CCCAGCGCCC CCTGCTAGTT GAGCGGGACA GGGGACCCTG TGTCTCACT
 GGGTCGCGGG GGACGATCAA CTCGCCCTGT CCCCTGGGAC ACAAGAGTGA
 26751 GTGATTTGCA ACTGTCTTAA CCCTGGATTA CATCAAGATC TTTGTTGCCA
 CACTAAACGT TGACAGGATT GGGACCTAAT GTAGTTCTAG AAACAACGGT
 26801 TCTCTGTGCT GAGTATAATA AATACAGAAA TTAAATATA CTGGGGCTCC
 AGAGACACGA CTCATATTAT TTATGTCTTT AATTTTATAT GACCCCGAGG
 26851 TATCGCCATC CTGTAAACGC CACCGTCTTC ACCCGCCCAA GCAAACCAAG
 ATAGCGGTAG GACATTTGCG GTGCAGAAAG TGGCGGGTT CGTTTGTTTC
 26901 GCGAACCTTA CCTGGTACTT TTAACATCTC TCCCTCTGTG ATTTACAACA
 CGCTTGGAAT GGACCATGAA AATTGTAGAG AGGGAGACAC TAAATGTTGT
 26951 GTTTCAACCC AGACGGAGTG AGTCTACGAG AGAACCTCTC CGAGCTCAGC
 CAAAGTTGGG TCTGCCTCAC TCAGATGCTC TCTTGGAGAG GCTCGAGTCG
 27001 TACTCCATCA GAAAAACAC CACCCTCCTT ACCTGCCGGG AACGTACGAG
 ATGAGGTAGT CTTTTTTGTG GTGGGAGGAA TGGACGGCCC TTGCATGCTC
 27051 TGCGTCACCG GCCGCTGCAC CACACCTACC GCCTGACCGT AAACCAGACT
 ACGCAGTGGC CGGCACGCTG GTGTGGATGG CGGACTGGCA TTTGGTCTGA
 27101 TTTTCCGGAC AGACCTCAAT AACTCTGTTT ACCAGAACAG GAGGTGAGCT
 AAAAGGCCCTG TCTGGAGTTA TTGAGACAAA TGGTCTTGTC CTCCACTCGA
 27151 TAGAAAACCC TTAGGGTATT AGGCCAAAGG CGCAGCTACT GTGGGGTTTA
 ATCTTTTGGG AATCCCATAA TCCGGTTTCC GCGTCGATGA CACCCCAAAT
 27201 TGAACAATTC AAGCAACTCT ACGGGCTATT CTAATTCAGG TTTCTCTAGA
 ACTTGTTAAG TTCGTTGAGA TGCCCGATAA GATTAAGTCC AAAGAGATCT
 27251 ATCGGGGTTG GGGTTATTCT CTGTCTTGTG ATTCTCTTTA TTCTTATACT
 TAGCCCCAAC CCCAATAAGA GACAGAACAC TAAGAGAAAT AAGAATATGA
 27301 AACGCTTCTC TGCCTAAGGC TCGCCGCCCTG CTGTGTGCAC ATTTGCATTT
 TTGCGAAGAG ACGGATTCCG AGCGGCGGAC GACACACGTG TAAACGTAAA
 27351 ATTGTACGCT TTTTAAACGC TGGGGTCGCC ACCCAAGATG ATTAGGTACA
 TAACAGTCGA AAAATTGCG ACCCCAGCGG TGGGTCTAC TAATCCATGT
 27401 TAATCTTAGG TTTACTCACC CTTGCGTCAG CCCACGGTAC CACCCAAAAG
 ATTAGGATCC AAATGAGTGG GAACGCAGTC GGGTGCCATG GTGGGTTTTTC

Figure 27AC

27451 GTGGATTTTA A G C C A G C C T G T A A T G T T A C A T T C G C A G C T G A A G C A
CACCTAAAAT TCCTCGGTGC GACATTACAA TGTAAGCGTC GACTTCGATT

27501 TGAGTGCACC ACTCTTATAA AATGCACCAC AGAACATGAA AAGCTGCTTA
ACTCACGTGG TGAGAATATT TTACGTGGTG TCTTGACTT TTCGACGAAT

27551 TTCGCCACAA AAACAAAATT GGCAAGTATG CTGTTTATGC TATTGGCAG
AAGCGGTGTT TTTGTTTTAA CCGTTCATAC GACAAATACG ATAAACCGTC

27601 CCAGGTGACA CTACAGAGTA TAATGTTACA GTTTCCAGG GTAAAAGTCA
GGTCCACTGT GATGTCTCAT ATTACAATGT CAAAAGGTCC CATTTCAGT

27651 TAAAACTTTT ATGTATACTT TTCCATTTTA TGAAATGTGC GACATTACCA
ATTTTGAAAA TACATATGAA AAGGTAAAAT ACTTTACACG CTGTAATGGT

27701 TGTACATGAG CAAACAGTAT AAGTTGTGGC CCCACAAAA TTGTGTGGAA
ACATGTACTC GTTGTCTATA TTCAACACCG GGGGTGTTT AACACACCTT

27751 AACACTGGCA CTTTCTGCTG CACTGCTATG CTAATTACAG TGCTCGCTTT
TTGTGACCGT GAAAGACGAC GTGACGATAC GATTAATGTC ACGAGCGAAA

27801 GGTCTGTACC CTACTCTATA TTAATAACAA AAGCAGACGC AGCTTTATTG
CCAGACATGG GATGAGATAT AATTATGTT TTCGTCTGCG TCGAAATAAC

27851 AGGAAAAGAA AATGCCTTAA TTTACTAAGT TACAAAGCTA ATGTCACCAC
TCCTTTTCTT TTACGGAATT AAATGATTCA ATGTTTCGAT TACAGTGGTG

27901 TAACTGCTTT ACTCGCTGCT TGCAAAACAA ATTCAAAAAG TTAGCATTAT
ATTGACGAAA TGAGCGACGA ACGTTTGTG TAAGTTTTTC AATCGTAATA

27951 AATTAGAATA GGATTTAAAC CCCCCGGTCA TTTCTGCTC AATACCATTTC
TTAATCTTAT CCTAAATTTG GGGGGCCAGT AAAGGACGAG TTATGGTAAG

28001 CCCTGAACAA TTGACTCTAT GTGGGATATG CTCCAGCGCT ACAACCTTGA
GGGACTTGTT AACTGAGATA CACCTATAC GAGGTGCGA TGTGGAAC

28051 AGTCAGGCTT CCTGGATGTC AGCATCTGAC TTTGGCCAGC ACCTGTCCCG
TCAGTCCGAA GGACCTACAG TCGTAGACTG AAACCGGTCG TGGACAGGGC

28101 CGGATTTGTT CCAGTCCAAC TACAGCGACC CACCCTAACA GAGATGACCA
GCCTAAACAA GGTGAGTTG ATGTCGCTGG GTGGGATTGT CTCTACTGGT

28151 ACACAACCAA CGCGGCCGCC GCTACCGGAC TTACATCTAC CACAAATACA
TGTGTTGGTT GCGCCGGCGG CGATGGCCTG AATGTAGATG GTGTTTATGT

28201 CCCCAAGTTT CTGCCTTTGT CAATAACTGG GATAACTTGG GCATGTGGTG
GGGGTTCAAA GACGGAAACA GTTATTGACC CTATTGAACC CGTACACCAC

28251 GTTCTCCATA GCGCTTATGT TTGTATGCCT TATTATTATG TGGCTCATCT
CAAGAGGTAT CGCGAATACA AACATACGGA ATAATAATAC ACCGAGTAGA

28301 GCTGCCTAAA GCGCAAACGC GCCCGACCAC CCATCTATAG TCCCATCATT
CGACGGATTT CGCGTTTGGC CGGGCTGGTG GGTAGATATC AGGGTAGTAA

28351 GTGCTACACC CAAACAATGA TGGAAATCCAT AGATTGGACG GACTGAAACA
CACGATGTGG GTTGTACT ACCTTAGGTA TCTAACCTGC CTGACTTTGT

Figure 27A D

28401 CATGTTCTTT TTTTACAG TATGATTAAA TGAGACATGA TTCTCTCTT
 GTACAAGAAA AGAGAATGTC ATACTAATTT ACTCTGTACT AAGGAGCTCA
 28451 TTTTATATTA CTGACCCTTG TTGCGCTTTT TTGTGCGTGC TCCACATTGG
 AAAATATAAT GACTGGGAAC AACGCGAAAA AACACGCACG AGGTGTAACC
 28501 CTGCGGTTTC TCACATCGAA GTAGACTGCA TTCCAGCCTT CACAGTCTAT
 GACGCCAAAG AGTGTAGCTT CATCTGACGT AAGGTCGGAA GTGTCAGATA
 28551 TTGCTTTACG GATTTGTAC CCTCACGCTC ATCTGCAGCC TCATCACTGT
 AACGAAATGC CTAAACAGTG GGAGTGCGAG TAGACGTCGG AGTAGTGACA
 28601 GGTCAATGCC TTTATCCAGT GCATTGACTG GGTCTGTGTG CGCTTTGCAT
 CCAGTAGCGG AAATAGGTCA CGTAACTGAC CCAGACACAC GCGAAACGTA
 28651 ATCTCAGACA CCATCCCCAG TACAGGGACA GGACTATAGC TGAGCTTCTT
 TAGAGTCTGT GGTAGGGGTC ATGTCCCTGT CCTGATATCG ACTCGAAGAA
 28701 AGAATTCCTT AATTATGAAA TTTACTGTGA CTTTCTGTCT GATTATTGCG
 TCTTAAGAAA TTAATACTTT AAATGACACT GAAAAGACGA CTAATAAACG
 28751 ACCCTATCTG CGTTTTGTTC CCCGACCTCC AAGCCTCAAA GACATATATC
 TGGGATAGAC GCAAAAACAAG GGGCTGGAGG TTCGGAGTTT CTGTATATAG
 28801 ATGCAGATTC ACTCGTATAT GGAATATTC AAGTTGCTAC AATGAAAAAA
 TACGTCTAAG TGAGCATATA CCTTATAAGG TTCAACGATG TTACTTTTTT
 28851 GCGATCTTTC CGAAGCCTGG TTATATGCAA TCATCTCTGT TATGGTGTTC
 CGCTAGAAAG GCTTCGGACC AATATACGTT AGTAGAGACA ATACCACAAG
 28901 TGCAGTACCA TCTTAGCCCT AGCTATATAT CCCTACCTTG ACATTGGCTG
 ACGTCATGGT AGAATCGGGA TCGATATATA GGGATGGAAC TGTAAACCGAC
 28951 GAACGCAATA GATGCCATGA ACCACCCAAC TTTCCCCGCG CCCGCTATGC
 CTGCGTTAT CTACGGTACT TGGTGGGTTG AAAGGGGCGC GGGCGATACG
 29001 TTCCACTGCA ACAAGTTGTT GCCGGCGGCT TTGTCCAGC CAATCAGCCT
 AAGGTGACGT TGTTCACAA CGGCCGCCGA AACAGGGTCG GTTAGTCGGA
 29051 CGCCCACCTT CTCCCACCCC CACTGAAATC AGCTACTTTA ATCTAACAGG
 GCGGGTGGAA GAGGGTGGGG GTGACTTTAG TCGATGAAT TAGATTGTCC
 29101 AGGAGATGAC TGACACCCTA GATCTAGAAA TGGACGGAAT TATTACAGAG
 TCCTCTACTG ACTGTGGGAT CTAGATCTTT ACCTGCCTTA ATAATGTCTC
 29151 CAGCGCCTGC TAGAAAGACG CAGGGCAGCG GCCGAGCAAC AGCGCATGAA
 GTGCGGACG ATCTTTCTGC GTCCCGTCGC CGGCTCGTTG TCGCGTACTT
 29201 TCAAGAGCTC CAAGACATGG TTAAGTTGCA CCAGTGCAAA AGGGGTATCT
 AGTTCTCGAG GTTCTGTACC AATTGAACGT GGTACGTTT TCCCCATAGA
 29251 TTTGTCTCGT AAAGCAGGCC AAAGTCACCT ACGACAGTAA TACCACCGGA
 AAACAGAGCA TTTCGTCCGG TTTCAGTGA TGCTGTCATT ATGGTGGCCT
 29301 CACCGCCTTA GCTACAAGTT GCCAACCAAG CGTCAGAAAT TGGTGGTCAT
 GTGGCGGAAT CGATGTTCAA CGGTTGGTTC GCAGTCTTTA ACCACCAGTA

Figure 27 A E

29351 GGTGGGAGAA A C CATT A CCATAACTCA GCACTCGGTA GAAACC G
CCACCTCTT TTCGGTAAT GGTATTGAGT CGTGAGCCAT CTTTGGCTTC

29401 GCTGCATTCA CTCACCTTGT CAAGGACCTG AGGATCTCTG CACCCTTATT
CGACGTAAGT GAGTGAACA GTTCTGGAC TCCTAGAGAC GTGGGAATAA

29451 AAGACCCCTGT GCGGTCTCAA AGATCTTATT CCCTTTAACT AATAAAAAA
TTCTGGGACA CGCCAGAGTT TCTAGAATAA GGGAAATTGA TTATTTTTTT

29501 AATAATAAAG CATCACTTAC TTAAAATCAG TTAGCAAATT TCTGTCCAGT
TTATTATTTC GTAGTGAATG AATTTTAGTC AATCGTTTAA AGACAGGTCA

29551 TTATTCAGCA GCACCTCCTT GCCCTCCTCC CAGCTCTGGT ATTGCAGCTT
AATAAGTCGT CGTGGAGGAA CGGGAGGAGG GTCGAGACCA TAACGTCGAA

29601 CCTCTGGCT GCAAACCTTC TCCACAATCT AAATGGAATG TCAGTTTCCT
GGAGGACCGA CGTTTGAAAG AGGTGTAGA TTTACCTTAC AGTCAAAGGA

29651 CCTGTTCCTG TCCATCCGCA CCCACTATCT TCATGTTGTT GCAGATGAAG
GGACAAGGAC AGGTAGGCGT GGGTGATAGA AGTACAACAA CGTCTACTTC

29701 CGCGCAAGAC CGTCTGAAGA TACCTTCAAC CCCGTGTATC CATATGACAC
GCGCGTTCTG GCAGACTTCT ATGGAAGTTG GGGCACATAG GTATACTGTG

29751 GGAAACCGGT CCTCCAACG TGCTTTTCT TACTCCTCCC TTTGTATCCC
CCTTTGGCCA GGAGGTTGAC ACGGAAAAGA ATGAGGAGGG AAACATAGGG

29801 CCAATGGGT TCAAGAGAGT CCCCCTGGGG TACTCTCTTT GCGCCTATCC
GGTTACCCAA AGTTCTCTCA GGGGGACCCC ATGAGAGAAA CGCGGATAGG

29851 GAACCTCTAG TTACCTCCAA TGGCATGCTT GCGCTCAAAA TGGGCAACGG
CTTGGAGATC AATGGAGGTT ACCGTACGAA CGCGAGTTT ACCCGTTGCC

29901 CCTCTCTCTG GACGAGGCCG GCAACCTTAC CTCCCAAAT GTAACCACTG
GGAGAGAGAC CTGCTCCGGC CGTTGGAATG GAGGGTTTTA CATTGGTGAC

29951 TGAGCCCACC TCTCAAAAA ACCAAGTCAA ACATAAACCT GGAAATATCT
ACTCGGGTGG AGAGTTTTTT TGGTTCAGTT TGTATTGGA CTTTTATAGA

30001 GCACCCCTCA CAGTTACCTC AGAAGCCCTA ACTGTGGCTG CCGCCGACCC
CGTGGGGAGT GTCAATGGAG TCTTCGGGAT TGACACCGAC GCGGGCGTGG

30051 TCTAATGGTC GCGGGCAACA CACTCACCAT GCAATCACAG GCCCCGCTAA
AGATTACCAG CGCCCGTTGT GTGAGTGGTA CGTTAGTGTC CGGGGCGATT

30101 CCGTGACGA CTCCAACTT AGCATTGCCA CCCAAGGACC CCTCACAGTG
GGCAGTGCT GAGGTTTGAA TCGTAACGGT GGGTTCCTGG GGAGTGTAC

30151 TCAGAAGGAA AGCTAGCCCT GCAAACATCA GGGCCCTCA CCACCACCGA
AGTCTTCCTT TCGATCGGGA CGTTTGTAGT CCGGGGGAGT GGTGGTGGCT

30201 TAGCAGTACC CTTACTATCA CTGCCTCACC CCCTCTAACT ACTGCCACTG
ATCGTCATGG GAATGATAGT GACGGAGTGG GGGAGATTGA TGACGGTGAC

30251 GTAGCTTGGG CATTGACTTG AAAGAGCCCA TTTATACACA AAATGGAAAA
CATCGAACCC GTAACGTAAC TTTCTCGGGT AAATATGTGT TTTACCTTTT

Figure 27 AF

30301 CTAGGACTAA ACGGGGC TCCTTTGTCAT GTAACAGACG ACCTAA C
 GATCCTGATT TCGCCCCG AGGAAACGTA CATGTGCTGC TGGATTGTC
 30351 TTTGACCGTA GCAACTGGTC CAGGTGTGAC TATTAATAAT ACTTCCTTGC
 AAAGTGGCAT CGTTGACCAG GTCCACACTG ATAATTATTA TGAAGGAACG
 30401 AAATAAAGT TACTGGAGCC TTGGGTTTTG ATTCACAAGG CAATATGCAA
 TTTGATTTCA ATGACCTCGG AACCCAAAAC TAAGTGTTCG GTTATACGTT
 30451 CTTAATGTAG CAGGAGGACT AAGGATTGAT TCTCAAAACA GACGCCTTAT
 GAATTACATC GTCCTCCTGA TTCCTAATA AGAGTTTTGT CTGCGGAATA
 30501 ACTTGATGTT AGTTATCCGT TTGATGCTCA AAACCAACTA AATCTAAGAC
 TGAATAACAA TCAATAGGCA AACTACGAGT TTTGGTTGAT TTAGATTCTG
 30551 TAGGACAGGG CCCTCTTTT ATAACTCAG CCCACAACCT GGATATTAAAC
 ATCTGTCCC GGGAGAAAAA TATTTGAGTC GGGTGTGAA CCTATAATTG
 30601 TACAACAAAG GCCTTTACTT GTTTACAGCT TCAAACAATT CAAAAAGCT
 ATGTTGTTTC CGGAAATGAA CAAATGTGCA AGTTTGTTAA GGTTTTTCGA
 30651 TGAGGTTAAC CTAAGCACTG CCAAGGGGTT GATGTTTGAC GCTACAGCCA
 ACTCCAATTG GATTCGTGAC GGTCCCCAA CTACAACTG CGATGTCGGT
 30701 TAGCCATTAA TGCAGGAGAT GGGCTTGAAT TTGGTTCACC TAATGCACCA
 ATCGGTAATT ACGTCCTCTA CCCGAACCTA AACCAAGTGG ATTACGTGGT
 30751 AACACAAATC CCCTCAAAAC AAAAATTGGC CATGGCCTAG AATTTGATTC
 TTGTGTTTAG GGGAGTTTTC TTTTAAACCG GTACCGGATC TTAACTAAG
 30801 AAACAAGGCT ATGTTTCCTA AACTAGGAAC TGGCCTTAGT TTTGACAGCA
 TTTGTTCCGA TACCAAGGAT TTGATCCTTG ACCGGAATCA AAAGTGTGCT
 30851 CAGGTGCCAT TACAGTAGGA AACAAAAATA ATGATAAGCT AACTTTGTGG
 GTCCACGGTA ATGTCATCCT TTGTTTTTAT TACTATTGCA TTGAAACACC
 30901 ACCACACCAG CTCCATCTCC TAACTGTAGA CTAAATGCAG AGAAAGATGC
 TGGTGTGGTC GAGGTAGAGG ATTGACATCT GATTTACGTC TCTTTCTACG
 30951 TAACTCACT TTGGTCTTAA CAAAATGTGG CAGTCAAATA CTGCTACAG
 ATTTGAGTGA AACCAGAATT GTTTTACACC GTCAGTTTAT GAACGATGTC
 31001 TTTCACTTTT GGCTGTAA AAGCAGTTTG CTCCAATATC TGGAACAGTT
 AAAGTCAAAA CCGACAATTT CCGTCAAACC GAGGTTATAG ACCTTGTCAG
 31051 CAAAGTGCTC ATCTTATTAT AAGATTTGAC GAAAATGGAG TGCTACTAAA
 GTTTCACGAG TAGAATAATA TTCTAACTG CTTTACCTC ACGATGATTT
 31101 CAATTCCTTC CTGGACCCAG AATATTGGA CTTTAGAAT GGAGATCTTA
 GTTAAGGAAG GACCTGGGTC TTATAACCTT GAAATCTTTA CCTCTAGAAT
 31151 CTGAAGGCAC AGCCTATACA AACGCTGTTG GATTTATGCC TAACCTATCA
 GACTTCCGTG TCGGATATGT TTGCGACAAC CTAAATACGG ATTGGATAGT
 31201 GCTTATCCAA AATCTCACGG TAAACTGCC AAAAGTAACA TTGTCAGTCA
 CGAATAGGTT TTAGAGTGCC ATTTTGACGG TTTTCATTGT AACAGTCAGT

Figure 27 AG

31251 AGTTTACTTA AAGGAGACA AAACATAACC TGTAACACTA ACCATTAC
 TCAAAATGAAT TTGCTCTGT TTTGATTGG ACATTGTGAT TGGTAATGTG
 31301 TAAACGGTAC ACAGGAAACA GGAGACACAA CTCCAAGTGC ATACTCTATG
 ATTTGCCATG TGTCTTTGT CCTCTGTGT GAGGTTCACG TATGAGATAC
 31351 TCATTTTCAT GGGACTGGTC TGGCCACAAC TACATTAATG AAATATTTGC
 AGTAAAAGTA CCCTGACCAG ACCGGTGTG ATGTAATTAC TTTATAAACG
 31401 CACATCTCT TACACTTTTT CATACATTGC CCAAGAATAA AGAATCGTTT
 GTGTAGGAGA ATGTGAAAAA GTATGTAACG GGTCTTATT TCTTAGCAAA
 31451 GTGTTATGTT TCAACGTGTT TATTTTTCAA TTGCAGAAAA TTTCAAGTCA
 CACAATACAA AGTTGCACAA ATAAAAAGTT AACGTCTTTT AAAGTTCAGT
 31501 TTTTTCATTG AGTAGTATAG CCCCACCACC ACATAGCTTA TACAGATCAC
 AAAAAGTAAG TCATCATATC GGGGTGGTGG TGTATCGAAT ATGTCTAGTG
 31551 CGTACCTTAA TCAAACTCAC AGAACCTAG TATTCAACCT GCCACCTCCC
 GCATGGAATT AGTTTGAGTG TCTTGGGATC ATAAGTTGGA CGGTGGAGGG
 31601 TCCCAACACA CAGAGTACAC AGTCCTTCT CCCCAGGCTGG CCTTAAAAAG
 AGGGTTGTGT GTCTCATGTG TCAGGAAAGA GGGGCCGACC GGAATTTTTC
 31651 CATCATATCA TGGGTAAACG ACATATTCTT AGGTGTATA TTCCACACGG
 GTAGTATAGT ACCCATGTG TGTATAAGAA TCCACAATAT AAGGTGTGCC
 31701 TTTCCTGTG AGCCAAACGC TCATCAGTGA TATTAATAAA CTCCCCGGGC
 AAAGGACAGC TCGGTTTGG AGTAGTCACT ATAATTATTT GAGGGCCCCG
 31751 AGCTCACTTA AGTTCATGTC GCTGTCCAGC TGCTGAGCCA CAGGCTGCTG
 TCGAGTGAAT TCAAGTACAG CGACAGGTG ACGACTCGGT GTCCGACGAC
 31801 TCCAACCTGC GGTGCTTAA CGGGCGGCGA AGGAGAAGTC CACGCCTACA
 AGGTTGAACG CCAACGAATT GCCCGCCGCT TCCTCTTCAG GTGCGGATGT
 31851 TGGGGGTAGA GTCATAATCG TGCATCAGGA TAGGGCGGTG GTGCTGCAGC
 ACCCCCATCT CAGTATTAGC ACGTAGTCTT ATCCCGCCAC CACGACGTG
 31901 AGCGCGCGAA TAAACTGCTG CCGCGCGCGC TCCGTCTGTC AGGAATACAA
 TCGCGCGCTT ATTTGACGAC GCGCGCGCGC AGGCAGGACG TCCTTATGTT
 31951 CATGGCAGTG GTCTCCTCAG CGATGATTG CACCGCCCGC AGCATAAGGC
 GTACCGTCAC CAGAGGAGTC GCTACTAAGC GTGGCGGGCG TCGTATTCG
 32001 GCCTTGTCT CCGGGCACAG CAGCGCACCC TGATCTCACT TAAATCAGCA
 CGGAACAGGA GGCCCGTGTG GTCGCGTGG ACTAGAGTGA ATTTAGTCGT
 32051 CAGTAACTGC AGCACAGCAC CACAATATTG TTCAAAATCC CACAGTGCAA
 GTCATTGACG TCGTGTGCTG GTGTTATAAC AAGTTTTAGG GTGTCACGTT
 32101 GCGCTGTAT CCAAAGCTCA TGGCGGGGAC CACAGAACCC ACGTGGCCAT
 CCGCGACATA GGTTCGAGT ACCGCCCTG GTGTCTTGGG TGCACCGGTA
 32151 CATACCACAA GCGCAGGTAG ATTAAGTGGC GACCCCTCAT AAACACGCTG
 GTATGGTGT CCGCTCCATC TAATTCACCG CTGGGGAGTA TTTGTGCGAC

Figure 27AH

32201 GACATAAACA TCTCTTT TGGCATGTTG TAATTCACCA CCTCCC A
CTGTATTGT AATGGAGAAA ACCGTACAAC ATTAAGTGGT GGAGGGCCAT

32251 CCATATAAAC CTCTGATTAA ACATGGCGCC ATCCACCACC ATCCTAAACC
GGTATATTG GAGACTAATT TGTACCGCGG TAGGTGGTGG TAGGATTG

32301 AGCTGGCCAA AACCTGCCCC CCGGCTATAC ACTGCAGGGA ACCGGGACTG
TCGACCGGTT TTGGACGGGC GGCCGATATG TGACGTCCCT TGGCCCTGAC

32351 GAACAATGAC AGTGGAGAGC CCAGGACTCG TAACCATGGA TCATCATGCT
CTTGTACTG TCACCTCTCG GGTCTGAGC ATTGGTACCT AGTAGTACGA

32401 CGTCATGATA TCAATGTTGG CACAACACAG GCACACGTGC ATACACTTCC
GCAGTACTAT AGTTACAACC GTGTTGTGTC CGTGTGCACG TATGTGAAGG

32451 TCAGGATTAC AAGCTCCTCC CGCGTTAGAA CCATATCCCA GGAACAACC
AGTCCTAATG TTCGAGGAGG GCGCAATCTT GGTATAGGGT CCCTTGTGG

32501 CATTCCTGAA TCAGCGTAA TCCCACTG CAGGGAAGAC CTCGCACGTA
GTAAGGACTT AGTCGCATTT AGGGTGTGAC GTCCCTTCTG GAGCGTGCAT

32551 ACTCACGTTG TGCATTGTCA AAGTGTACA TTCGGGCAGC AGCGGATGAT
TGAGTGCAAC ACGTAACAGT TTCACAATGT AAGCCCGTCG TCGCCTACTA

32601 CCTCCAGTAT GGTAGCGCGG GTTCTGTCT CAAAAGGAGG TAGACGATCC
GGAGGTCATA CCATCGCGCC CAAAGACAGA GTTTCCTCC ATCTGCTAGG

32651 CTACTGTACG GAGTGCGCCG AGACAACCGA GATCGTGTG GTCGTAGTGT
GATGACATGC CTCACGCGGC TCTGTGGCT CTAGCACAA CAGCATCACA

32701 CATGCCAAAT GGAACGCCGG ACGTAGTCAT ATTCCTGAA GCAAAACCAG
GTACGGTTA CCTTGCGGCC TGCATCAGTA TAAAGGACTT CGTTTGGTC

32751 GTGCGGCGT GACAAACAGA TCTGCGTCTC CGGTCTCGCC GCTTAGATCG
CACGCCCGCA CTGTTGTCT AGACGCAGAG GCCAGAGCGG CGAATCTAGC

32801 CTCTGTGTAG TAGTTGTAGT ATATCCAATC TCTCAAAGCA TCCAGGCGCC
GAGACACATC ATCAACATCA TATAGGTGAG AGAGTTTCGT AGGTCCCGG

32851 CCCTGGCTTC GGGTCTATG TAACTCCTT CATGCGCCGC TGGCCTGATA
GGGACCGAAG CCCAAGATAC ATTTGAGGAA GTACGCGCGC ACGGCACTAT

32901 ACATCCACCA CCGCAGAATA AGCCACACCC AGCCAACCTA CACATTCGTT
TGTAAGTGGT GCGTCTTAT TCGGTGTGG TCGGTTGGAT GTGTAAGCAA

32951 CTGCGAGTCA CACACGGGAG GAGCGGAAG AGCTGGAAGA ACCATGTTTT
GACGCTCAGT GTGTGCCCTC CTCGCCCTT TCGACCTCT TGGTACAAAA

33001 TTTTTTTATT CAAAAGATT ATCCAAAACC TCAAATGAA GATCTATTAA
AAAAAATAA GGTTTTCTAA TAGGTTTGG AGTTTACTT CTAGATAATT

33051 GTGAACGCGC TCCCCTCCGG TGGCGTGGT AACTCTACA GCCAAAGAAC
CACTTGCGCG AGGGGAGGCC ACCGCACCAG TTTGAGATGT CGGTTTCTTG

33101 AGATAATGGC ATTTGTAAGA TGTGACAA TGGCTTCAA AAGGCAACG
TCTATTACCG TAAACATTCT ACAACGTGTT ACCGAAGGTT TTCCGTTTGC

Figure 27 AI

33151 GCCCTCACGT GTGGAC GTAAAGGCTA AACCCCTCAG TGTGAATTC
 CGGGAGTGCA GTTCACCTG CATTTCGGAT TTGGGAAGTC CCACCTTAG
 33201 CTCTATAAAC ATTCCAGCAC CTTCAACCAT GCCCAAATAA TTCTCATCTC
 GAGATATTTG TAAGGTCGTG GAAGTTGGTA CGGGTTTATT AAGAGTAGAG
 33251 GCCACCTTCT CAATATATCT CTAAGCAAAT CCCGAATATT AAGTCCGGCC
 CGGTGGAAGA GTTATATAGA GATTCTTTTA GGGCTTATAA TTCAGGCCGG
 33301 ATTGTAAAAA TCTGCTCCAG AGCGCCCTCC ACCTTCAGCC TCAAGCAGCG
 TAACATTTTT AGACGAGGTC TCGCGGGAGG TGGAACTCGG AGTTCGTCTG
 33351 AATCATGATT GCAAAAATTC AGGTTCTCTCA CAGACCTGTA TAAGATTCAA
 TTAGTACTAA CGTTTTTAAG TCCAAGGAGT GTCTGGACAT ATTCTAAGTT
 33401 AAGCGGAACA TTAACAAAAA TACCGCGATC CCGTAGGTCC CTTCGCAGGG
 TTCGCCCTGT AATTGTTTTT ATGGCGCTAG GGCATCCAGG GAAGCGTCCC
 33451 CCAGCTGAAC ATAATCGTGC AGGTCTGCAC GGACCAGCGC GGCCACTTCC
 GGTGACTTG TATTAGCAGC TCCAGACGTG CCTGGTCTCG CCGGTGAAGG
 33501 CCGCCAGGAA CCATGACAAA AGAACCACCA CTGATTATGA CACGCATACT
 GCGGTCCTT GGTACTGTTT TCTTGGGTGT GACTAATACT GTGCGTATGA
 33551 CGGAGCTATG CTAACCAGCG TAGCCCCGAT GTAAGCTTGT TGCATGGCG
 GCCTCGATAC GATTGGTCTG ATCGGGGCTA CATTGGAACA ACGTACCCGC
 33601 GCGATATAAA ATGCAAGGTG CTGCTCAAAA AATCAGGCAA AGCCTCGCGC
 CGCTATATTT TACGTTCAC GACGAGTTT TTAGTCCGTT TCGGAGCGCG
 33651 AAAAAAGAAA GCACATCGTA GTCATGCTCA TGCAGATAAA GGCAGGTAAG
 TTTTCTCTT CGTGTAGCAT CAGTACGAGT ACGTCTATTT CCGTCCATTC
 33701 CTCCGGAACC ACCACAGAAA AAGACACCAT TTTTCTCTCA AACATGTCTG
 GAGGCCCTTG TGGTGTCTTT TTCTGTGGTA AAAAGAGAGT TTGTACAGAC
 33751 CGGGTTTCTG CATAAACACA AAATAAAATA ACAAAAAAAC ATTTAAACAT
 GCCCAAAGAC GTATTTGTGT TTTATTTTAT TGTTTTTTTG TAAATTTGTA
 33801 TAGAAGCCTG TCTTACAACA GGAAAAACAA CCTTATAAG CATAAGACGG
 ATCTTCGGAC AGAATGTTGT CTTTTTGTG GGAATATTC GTATTCTGCC
 33851 ACTACGGCCA TGCCGGCGTG ACCGTAAAAA AACTGGTCAC CGTGATTAAA
 TGATGCCGGT ACGGCCGCAC TGGCATTTTT TTGACCACTG GCACTAATTT
 33901 AAGCACCACC GACAGCTCCT CGGTCATGTC CGGAGTCATA ATGTAAGACT
 TTCGTGGTGG CTGTCGAGGA GCCAGTACAG GCCTCAGTAT TACATTCTGA
 33951 CGGTAAACAC ATCAGGTTGA TTCACATCGG TCAGTGCTAA AAAGCGACCG
 GCCATTTGTG TAGTCCAAC TAAAGTAGCC AGTCACGATT TTTCGCTGGC
 34001 AAATAGCCCG GGGGAATACA TACCCGCAGG CGTAGAGACA ACATTACAGC
 TTTATCGGGC CCCCTTATGT ATGGGCGTCC GCATCTCTGT TGTAAATGTCG
 34051 CCCCATAGGA GGTATAACAA AATTAATAGG AGAGAAAAAC ACATAAACAC
 GGGGTATCCT CCATATTGTT TTAATTATCC TCTCTTTTTG TGTATTGTG

Figure 27A J

34101 CTGAAAAACC CCGTTGCCTA GGCAAAATAG CACCCTCCCG*GTGCATTA
 GACTTTTTCG GCGACGGAT CCGTTTATC GTGGGAGGGC GAGGTCCTT
 34151 ACATACAGCG CTTCCACAGC GGCAGCCATA ACAGTCAGCC TTACCAGTAA
 TGTATGTCGC GAAGGTGTCG CCGTCGGTAT TGTCAGTCGG AATGGTCATT
 34201 AAAAGAAAAC CTATTAAAAA AACACCACTC GACACGGCAC CAGCTCAATC
 TTTCTTTTG GATAATTTT TTGTGGTGAG CTGTGCCGTG GTCGAGTTAG
 34251 AGTCACAGTG TAAAAAAGGG CCAAGTGCAG AGCGAGTATA TATAGGACTA
 TCAGTGTAC ATTTTTTCCC GGTTCACGTC TCGTCTATAT ATATCCTGAT
 34301 AAAAATGACG TAACGGTTAA AGTCCACAAA AAACACCCAG AAAACCGCAC
 TTTTACGCG ATTGCCAATT TCAGGTGTTT TTTGTGGGTC TTTGGCGTG
 34351 GCGAACCTAC GCCCAGAAAC GAAAGCCAAA AAACCCACAA CTTCTCAAA
 CGCTTGGATG CCGGTCTTTG CTTTCGGTTT TTTGGGTGTT GAAGGAGTTT
 34401 TCGTCACTTC CGTTTTCCTA CGTTACGTCA CTTCCCATTT TAAGAAAAT
 AGCAGTGAAG GCAAAAGGGT GCAATGCAGT GAAGGGTAAA ATTCTTTGA
 34451 ACAATTCCCA ACACATACAA GTTACTCCGC CCTAAAACCT ACGTCACCCG
 TGTAAAGGGT TGTGTATGTT CAATGAGCGG GGATTTTGGA TGCAGTGGGC
 34501 CCCCCTTCCC ACGCCCCGCG CCACGTCAAA AACTCCACCC CCTCATTATC
 GGGCAAGGG TCGGGGCGC GGTGCAGTGT TTGAGGTGGG GGAGTAATAG
 PacI

 34551 ATATTGGCTT CAATCCAAAA TAAGGTATAT TATTGATGAT GTTAATTAAG
 TATAACCGAA GTTAGGTTTT ATTCCATATA ATAATACTA CAATTAATTC
 34601 AATTCGGATC TCGACGCGA GGCTGGATGG CCTTCCCAT TATGATTCTT
 TTAAGCCTAG ACGCTGCGCT CCGACCTACC GGAAGGGGTA ATACTAAGAA
 34651 CTCGCTTCCG GCGGCATCGG GATGCCCCGCG TTGCAGGCCA TGCTGTCCAG
 GAGCGAAGGC CCGCTAGGCC CTACGGGCGC AACGTCCGGT ACGACAGGTC
 34701 GCAGGTAGAT GACGACCATC AGGGACAGCT TCAAGGCCAG CAAAAGGCCA
 CGTCCATCTA CTGCTGGTAG TCCCTGTCGA AGTTCCGGTC GTTTTCCGGT
 34751 GGAACCGTAA AAAGGCCGCG TTGCTGGCGT TTTTCCATAG GCTCCGCCCC
 CCTTGGCATT TTTCCGGCGC AACGACCGCA AAAAGGTATC CGAGGCGGGG
 34801 CCTGACGAGC ATCACAACAAA TCGACGCTCA AGTCAGAGGT GGCGAAACCC
 GGACTGCTCG TAGTGTTTTT AGCTGCGAGT TCAGTCTCCA CCGCTTTGGG
 34851 GACAGGACTA TAAAGATACC AGGCGTTTCC CCCTGGAAGC TCCCTCGTGC
 CTGTCTGAT ATTTCTATGG TCCGCAAAGG GGGACCTTCG AGGGAGCACG
 34901 GCTCTCCTGT TCCGACCCTG CCGCTTACCG GATACCTGTC CGCCTTTCTC
 CGAGAGGACA AGGCTGGGAC GCGAATGGC CTATGGACAG GCGGAAAGAG
 34951 CCTTCGGGAA GCGTGGCGCT TTCTCATAGC TCACGCTGTA GGTATCTCAG
 GGAAGCCCTT CGCACC CGA AAGAGTATCG AGTCCGACAT CCATAGAGTC
 35001 TTCGGTGTAG GTCGTTGCT CCAAGCTGGG CTGTGTGCAC GAACCCCCCG
 AAGCCACATC CAGCAAGCGA GGTCGACCC GACACACGTG CTTGGGGGGC

Figure 27 AK

35051 TTCAGCCCGA CC~~G~~CTGCGCC TTATCCGGTA ACTATCGTCT TGAGTCC~~A~~AC
 AAGTCGGGCT GGCGACGCGG AATAGGCCAT TGATAGCAGA ACTCAGGTTG
 35101 CCGGTAAGAC ACGACTTATC GCCACTGGCA GCAGCCACTG GTAACAGGAT
 GGCCATTCTG TGCTGAATAG CGGTGACCGT CGTCGGTGAC CATGTGCTTA
 35151 TAGCAGAGCG AGGTATGTAG GCGGTGCTAC AGAGTTCTTG AAGTGGTGGC
 ATCGTCTCGC TCCATACATC CGCCACGATG TCTCAAGAAC TTCACCACCG
 35201 CTA~~A~~CTACGG CTACACTAGA AGGACAGTAT TTGGTATCTG CGCTCTGCTG
 GATTGATGCC GATGTGATCT TCCTGTCATA AACCATAGAC GCGAGACGAC
 35251 AAGCCAGTTA CCTTCGGAAA AAGAGTTGGT AGCTCTTGAT CCGGCAAACA
 TTCGGTCAAT GGAAGCCTTT TTCTCAACCA TCGAGAACTA GGCCGTTTGT
 35301 AACCACCGCT GGTAGCGGTG GTTTTTTTGT TTGCAAGCAG CAGATTACGC
 TTGGTGGCGA CCATCGCCAC CAAAAAACA AACGTTGTC GTCTAATGCC
 35351 GCAGAAAAAA AGGATCTCAA GAAGATCCTT TGATCTTTTC TACGGGGTCT
 CGTCTTTTTT TCCTAGAGTT CTTCTAGGAA ACTAGAAAAG ATGCCCCAGA
 35401 GACGCTCAGT GGAACGAAAA CTCACGTAA GGGATTTTGG TCATGAGATT
 CTGCGAGTCA CCTTGCTTTT GAGTGCAATT CCCTAAAACC AGTACTCTAA
 35451 ATCAAAAAGG ATCTTCACCT AGATCCTTTT AAATCAATCT AAAGTATATA
 TAGTTTTTCC TAGAAGTGGA TCTAGGAAAA TTTAGTTAGA TTTCATATAT
 35501 TGAGTAAACT TGGTCTGACA GTTACCAATG CTTAATCAGT GAGGCACCTA
 ACTCATTTGA ACCAGACTGT CAATGGTTAC GAATTAGTCA CTCCGTGGAT
 35551 TCTCAGCGAT CTGTCTATTT CGTTCATCCA TAGTTGCCTG ACTCCCCGTC
 AGAGTCGCTA GACAGATAAA GCAAGTAGGT ATCAACGGAC TGAGGGGCAG
 35601 GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC CCA~~G~~TGCTGC
 CACATCTATT GATGCTATGC CCTCCGAAT GGTAGACCGG GGTCA~~C~~GACG
 35651 AATGATACCG CGAGACCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA
 TTACTATGGC GCTCTGGGTG CGAGTGGCCG AGGTCTAAAT AGTCGTATT
 35701 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC
 TGGTCGGTGC GCCTTCCCGG CTCGCGTCTT CACCAGGACG TTGAAATAGG
 35751 GCCTCCATCC AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC
 CGGAGGTAGG TCAGATAATT AACAACGGCC CTTGATCTC ATTCATCAAG
 35801 GCCAGTTAAT AGTTTGC~~G~~CA AC~~G~~TTGTTGC CATTGCTACA GGCATCGTGG
 CCGTCAATTA TCAAACGCGT TGCAACAACG GTAACGATGT CCGTAGCACC
 35851 TGTCACGCTC GTCGTTTGGT ATGGCTTCAT TCAGCTCCGG TTCCCAACGA
 ACAGTGC~~G~~AG CAGCAAACCA TACCGAAGTA AGTCGAGGCC AAGGTTGCT
 35901 TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG CGGTTAGCTC
 AGTTCCGCTC AATGTACTAG GGGGTACAAC ACGTTTTTTC GCCAATCGAG
 35951 CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGCCGCA GTGTTATCAC
 GAAGCCAGGA GGCTAGCAAC AGTCTTCATT CAACGGCGT CACAATAGTG

Figure 2 AL

36001 TCATGGTTAT ~~GG~~AGCACTG CATAATTCTC TTAAGTGCAT GCCATC ~~TA~~
 AGTACCAATA CCGTCGTGAC GTATTAAGAG AATGACAGTA CGGTAGGCAT
 36051 AGATGCTTTT CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA
 TCTACGAAAA GACACTGACC ACTCATGAGT TGGTTCAGTA AGACTCTTAT
 36101 GTGTATGCGG CGACCGAGTT GCTCTTGCCC GCGGTCAACA CGGGATAATA
 CACATACGCC GCTGGCTCAA CGAGAACGGG CCGCAGTTGT GCCCTATTAT
 36151 CCGCGCCACA TAGCAGAACT TTAAGAGTGC TCATCATTTG AAAACGTTCT
 GCGCGGTGT ATCGTCTTGA AATTTTCACG AGTAGTAACC TTTTGCAAGA
 36201 TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT CCAGTTCGAT
 AGCCCCGCTT TTGAGAGTTC CTAGAATGGC GACAACCTA GGTCAGGCTA
 36251 GTAACCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA
 CATTGGGTGA GCACGTGGGT TGAAGTAAG TCGTAGAAAA TGAAAGTGGT
 36301 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA
 CGCAAAGACC CACTCGTTTT TGTCCTTCCG TTTTACGGCG TTTTTCCTT
 36351 ATAAGGGCGA CACGGAATG TTGAATACTC ATACTCTTCC TTTTCAATA
 TATTTCCGCT TGCCCTTTAC AACTTATGAG TATGAGAAGG AAAAAGTTAT
 36401 TTATTGAAGC ATTTATCAGG GTTATTGTCT CATGAGCGGA TACATATTTG
 AATAACTTCG TAAATAGTCC CAATAACAGA GACTCGCCT ATGTATAAAC
 36451 AATGTATTTA GAAAAATAAA CAAATAGGGG TTCCGCGCAC ATTTCCCGA
 TTACATAAAT CTTTTATTT GTTTATCCCC AAGGCGCGTG TAAAGGGGCT
 36501 AAAGTGCCAC CTGACGTCTA AGAAACCATT ATTATCATGA CATTAACCTA
 TTTCACGGTG GACTGCAGAT TCTTTGGTAA TAATAGTACT GTAATTGGAT
 36551 TAAAAATAGG CGTATCACGA GGCCCTTTCG TCTTCAAGAA TTGGATCCGA
 ATTTTATTC GCATAGTGCT CCGGGAAGC AGAAGTTCTT AACCTAGGCT

PacI

36601 ATTCTTAATT TCTTAATTAA (SEQ ID NO:34)
 TAAGAATTAA AGAATTAATT (SEQ ID NO:35)

Figure 27AM

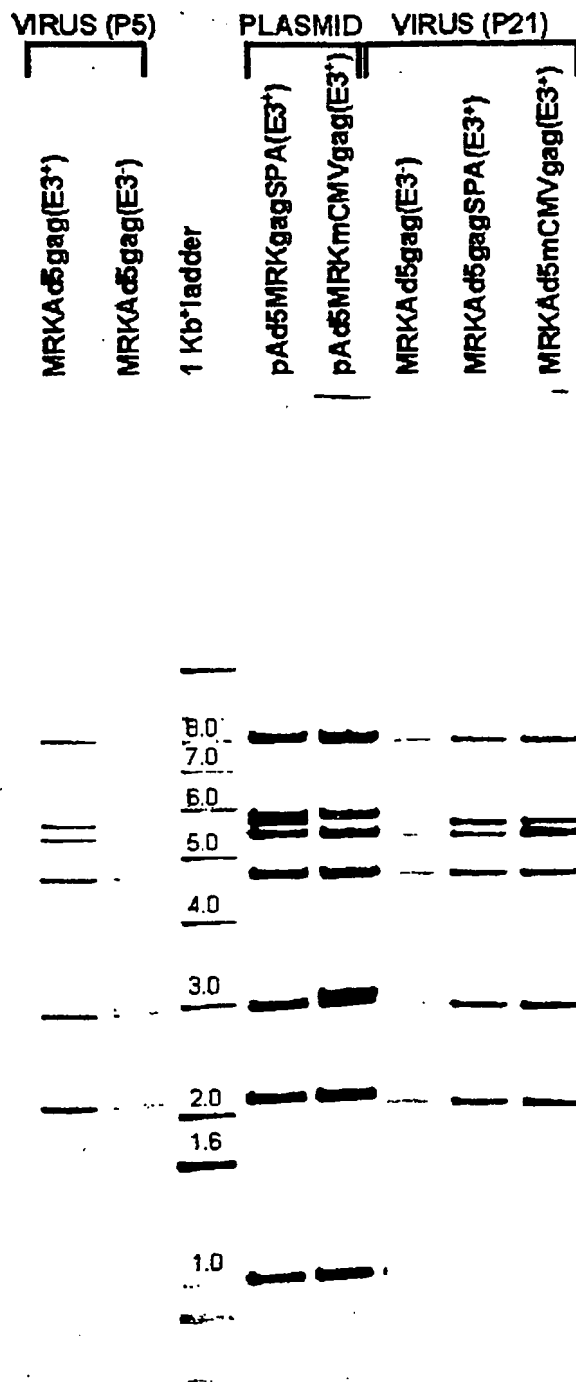


FIGURE 28

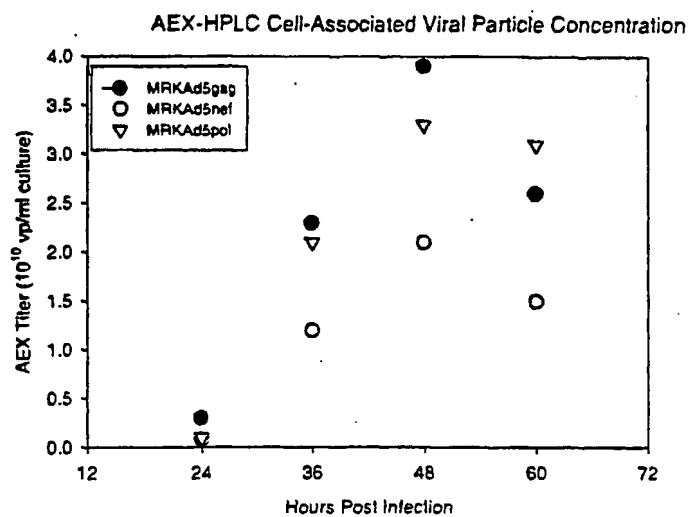


FIGURE 29A

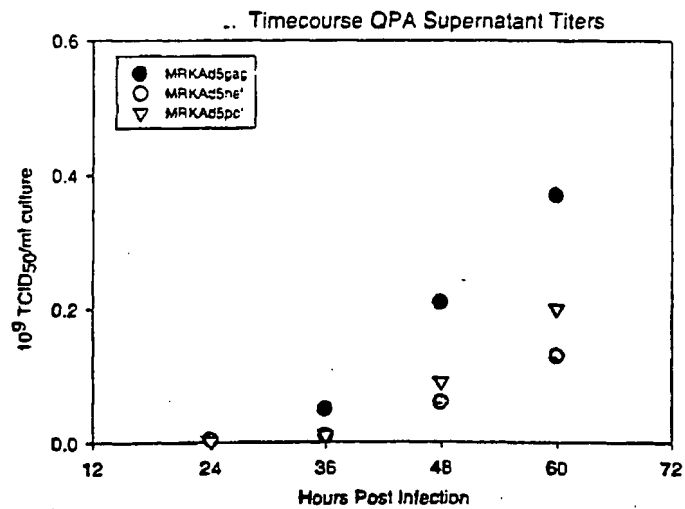


FIGURE 29B

atg gat gca atg aag aga ggg ctc tgc tgt gtg ctg ctg ctg tgt gga Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly 1 5 10 15	48
gca gtc ttc gtt tgc ccc agc gag atc tcc att gtg tgg gcc tcc agg Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ile Val Trp Ala Ser Arg 20 25 30	96
gag ctg gag agg ttt gct gtg aac cct ggc ctg ctg gag acc tct gag Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser Glu 35 40 45	144
ggg tgc agg cag atc ctg ggc cag ctc cag ccc tcc ctg caa aca ggc Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly 50 55 60	192
tct gag gag ctg agg tcc ctg tac aac aca gtg gct acc ctg tac tgt Ser Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys 65 70 75 80	240
gtg cac cag aag att gat gtg aag gac acc aag gag gcc ctg gag aag Val His Gln Lys Ile Asp Val Lys Asp Thr Lys Glu Ala Leu Glu Lys 85 90 95	288
att gag gag gag cag aac aag tcc aag aag aag gcc cag cag gct gct Ile Glu Glu Glu Gln Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala 100 105 110	336
gct ggc aca ggc aac tcc agc cag gtg tcc cag aac tac ccc att gtg Ala Gly Thr Gly Asn Ser Ser Gln Val Ser Gln Asn Tyr Pro Ile Val 115 120 125	384
cag aac ctc cag ggc cag atg gtg cac cag gcc atc tcc ccc cgg acc Gln Asn Leu Gln Gly Gln Met Val His Gln Ala Ile Ser Pro Arg Thr 130 135 140	432
ctg aat gcc tgg gtg aag gtg gtg gag gag aag gcc ttc tcc cct gag Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys Ala Phe Ser Pro Glu 145 150 155 160	480
gtg atc ccc atg ttc tct gcc ctg tct gag ggt gcc acc ccc cag gac Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr Pro Gln Asp 165 170 175	528
ctg aac acc atg ctg aac aca gtg ggg ggc cat cag gct gcc atg cag Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met Gln 180 185 190	576
atg ctg aag gag acc atc aat gag gag gct gct gag tgg gac agg ctg Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Leu 195 200 205	624
cat cct gtg cac gct ggc ccc att gcc ccc ggc cag atg agg gag ccc His Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro 210 215 220	672
agg ggc tct gac att gct ggc acc acc tcc acc ctc cag gag cag att Arg Gly Ser Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile 225 230 235 240	720
ggc tgg atg acc aac aac ccc ccc atc cct gtg ggg gaa atc tac aag Gly Trp Met Thr Asn Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys 245 250 255	768

Figure 30A'

agg tgg atc atc ctg ggc ctg aac aag att gtg agg atg tac tcc ccc Arg Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg Met Tyr Ser Pro 260 265 270	816
acc tcc atc ctg gac atc agg cag ggc ccc aag gag ccc ttc agg gac Thr Ser Ile Leu Asp Ile Arg Gln Gly Pro Lys Glu Pro Phe Arg Asp 275 280 285	864
tat gtg gac agg ttc tac aag acc ctg agg gct gag cag gcc tcc cag Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala Glu Gln Ala Ser Gln 290 295 300	912
gag gtg aag aac tgg atg aca gag acc ctg ctg gtg cag aat gcc aac Glu Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln Asn Ala Asn 305 310 315 320	960
cct gac tgc aag acc atc ctg aag gcc ctg ggc cct gct gcc acc ctg Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr Leu 325 330 335	1008
gag gag atg atg aca gcc tgc cag ggg gtg ggg ggc cct ggt cac aag Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys 340 345 350	1056
gcc agg gtg ctg gct gag gcc atg tcc cag gtg acc aac tcc gcc acc Ala Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Ser Ala Thr 355 360 365	1104
atc atg atg cag agg ggc aac ttc agg aac cag agg aag aca gtg aag Ile Met Met Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Thr Val Lys 370 375 380	1152
tgc ttc aac tgt ggc aag gtg ggc cac att gcc aag aac tgt agg gcc Cys Phe Asn Cys Gly Lys Val Gly His Ile Ala Lys Asn Cys Arg Ala 390 395 400	1200
ccc agg aag aag ggc tgc tgg aag tgt ggc aag gag ggc cac cag atg Pro Arg Lys Lys Gly Cys Trp Lys Cys Gly Lys Glu Gly His Gln Met 405 410 415	1248
aag gac tgc aat gag agg cag gcc aac ttc ctg ggc aaa atc tgg ccc Lys Asp Cys Asn Glu Arg Gln Ala Asn Phe Leu Gly Lys Ile Trp Pro 420 425 430	1296
tcc cac aag ggc agg cct ggc aac ttc ctc cag tcc agg cct gag ccc Ser His Lys Gly Arg Pro Gly Asn Phe Leu Gln Ser Arg Pro Glu Pro 435 440 445	1344
aca gcc cct ccc gag gag tcc ttc agg ttt ggg gag gag aag acc acc Thr Ala Pro Pro Glu Glu Ser Phe Arg Phe Gly Glu Glu Lys Thr Thr 450 455 460	1392
ccc agc cag aag cag gag ccc att gac aag gag ctg tac ccc ctg gcc Pro Ser Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu Ala 465 470 475 480	1440
tcc ctg agg tcc ctg ttt ggc aac gac ccc tcc tcc cag taa (SID NO:36) 1482 Ser Leu Arg Ser Leu Phe Gly Asn Asp Pro Ser Ser Gln * (SID NO:37) 485 490	

Figure 30 B

Figure 31

IFN- γ Secretion against Gag 20-aa pool from CD3⁺ T cells of Monkey PBMCs

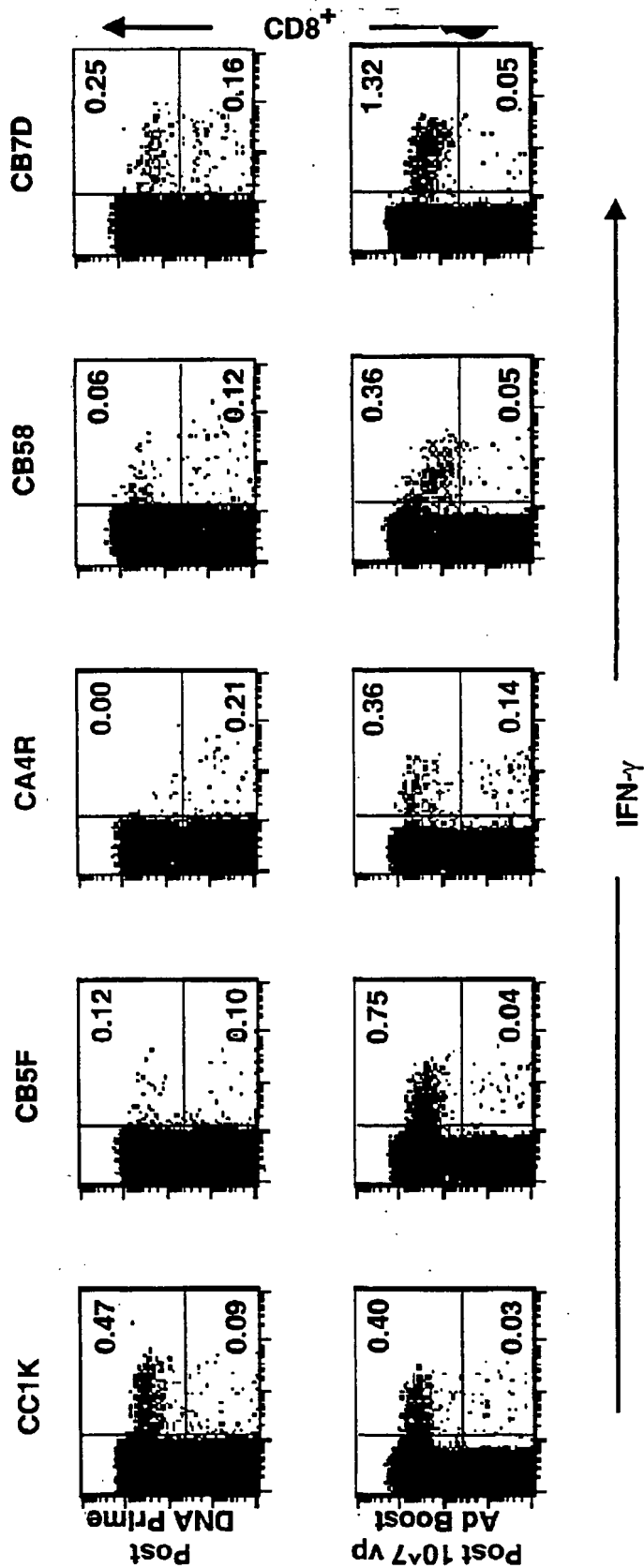


FIGURE 32

Comparison of Single-Modality Adenovirus Immunization with DNA+Adjuvant Prime/Adenovirus Boost

Immunizations

Ad Prime/Boost

DNA-CRL1005 Prime/Ad Boost

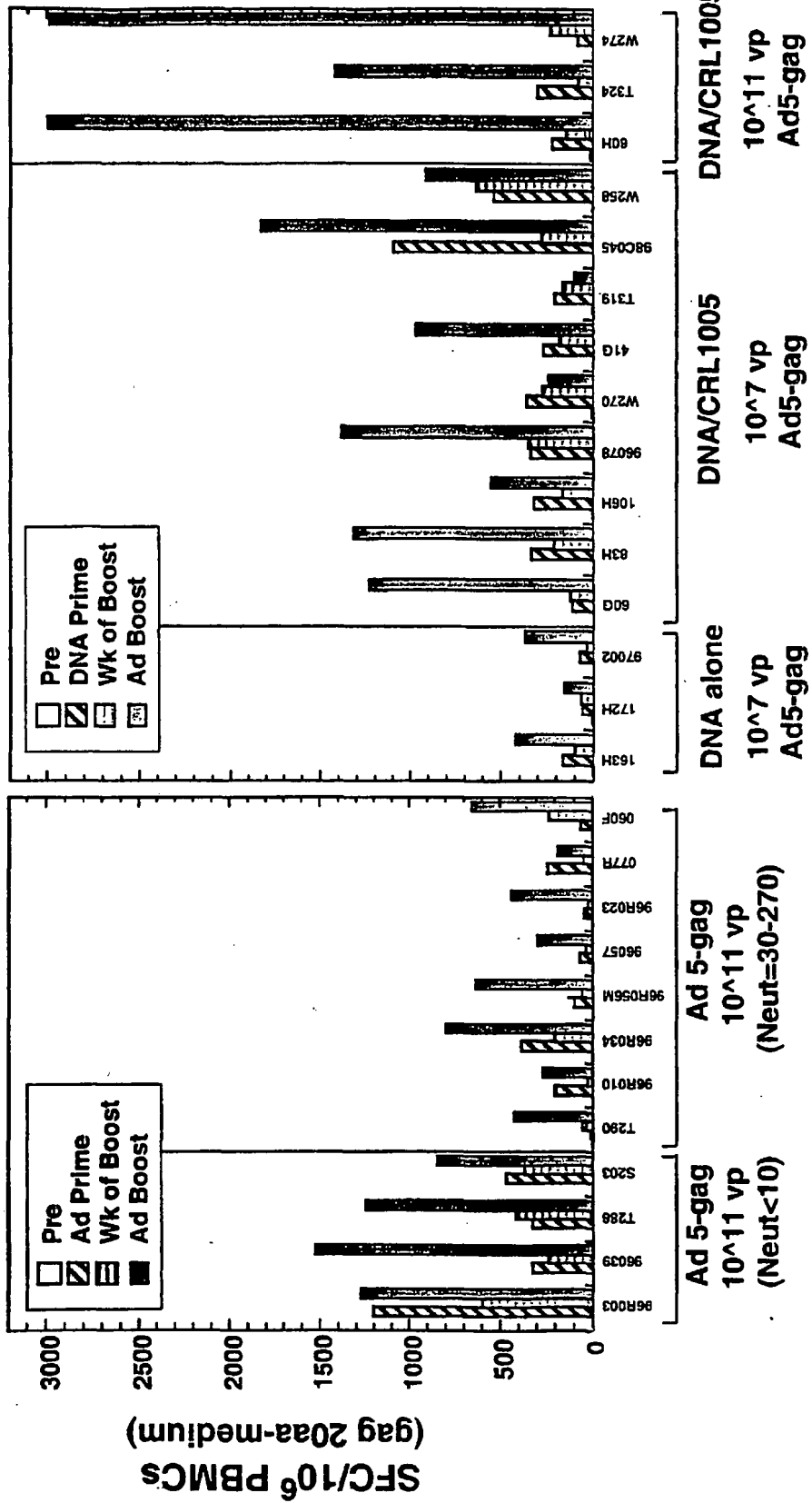


FIGURE 33A

ATGGGTGCTA GGGCTTCTGT GCTGTCTGGT GGTGAGCTGG ACAAGTGGGA GAAGATCAGG
 CTGAGGCCTG GTGGCAAGAA GAAGTACAAG CTAAAGCACA TTGTGTGGGC CTCCAGGGAG
 CTGGAGAGGT TTGCTGTGAA CCCTGGCCTG CTGGAGACCT CTGAGGGGTG CAGGCAGATC
 CTGGGCCAGC TCCAGCCCTC CCTGCAACA GGCTCTGAGG AGCTGAGGTC CCTGTACAAC
 ACAGTGGCTA CCCTGTACTG TGTGCACCAG AAGATTGATG TGAAGGACAC CAAGGAGGCC
 CTGGAGAAGA TTGAGGAGGA GCAGAACAAG TCCAAGAAGA AGGCCAGCA GGCTGCTGCT
 GGCACAGGCA ACTCCAGCCA GGTGTCCCAG AACTACCCCA TTGTGCAGAA CCTCCAGGGC
 CAGATGGTGC ACCAGGCCAT CCCCCCGG ACCCTGAATG CCTGGGTGAA GGTGGTGGAG
 GAGAAGGCCT TCTCCCTGA GGTGATCCCC ATGTTCTCTG CCCTGTCTGA GGGTGCCACC
 CCCCAGGACC TGAACACCAT GCTGAACACA GTGGGGGGCC ATCAGGCTGC CATGCAGATG
 CTGAAGGAGA CCATCAATGA GGAGGCTGCT GAGTGGGACA GGCTGCATCC TGTGCACGCT
 GGCCCCATTG CCCCCGGCCA GATGAGGGAG CCCAGGGGCT CTGACATTGC TGGCACCACC
 TCCACCCTCC AGGAGCAGAT TGGCTGGATG ACCAACAACC CCCCATCCC TGTGGGGGAA
 ATCTACAAGA GGTGGATCAT CCTGGGCCTG AACAAGATTG TGAGGATGTA CTCCCCACC
 TCCATCCTGG ACATCAGGCA GGGCCCCAAG GAGCCCTTCA GGGACTATGT GGACAGGTTT
 TACAAGACCC TGAGGGCTGA GCAGGCCTCC CAGGAGGTGA AGAACTGGAT GACAGAGACC
 CTGTGGTGC AGAATGCCAA CCCTGACTGC AAGACCATCC TGAAGGCCCT GGGCCCTGCT
 GCCACCCTGG AGGAGATGAT GACAGCCTGC CAGGGGGTGG GGGGCCCTGG TCACAAGGCC
 AGGGTGCTGG CTGAGGCCAT GTCCCAGGTG ACCAACTCCG CCACCATCAT GATGCAGAGG
 GGCAACTTCA GGAACCAGAG GAAGACAGTG AAGTGCTTCA ACTGTGGCAA GGTGGGCCAC
 ATTGCCAAGA ACTGTAGGGC CCCCAGGAAG AAGGGCTGCT GGAAGTGTGG CAAGGAGGGC
 CACCAGATGA AGGACTGCAA TGAGAGGCAG GCCAACTTCC TGGGCAAAAT CTGGCCCTCC
 CACAAGGGCA GGCCTGGCAA CTTCTCCAG TCCAGGCCTG AGCCCACAGC CCCTCCCGAG
 GAGTCTTCA GGTTTGGGGA GGAGAAGACC ACCCCCAGCC AGAAGCAGGA GCCCATTGAC
 AAGGAGCTGT ACCCCCTGGC CTCCCTGAGG TCCTGTTTG GCAACGACCC CTCCTCCAG
 ATGGCTCCCA TCTCCCCAT TGAGACTGTG CCTGTGAAGC TGAAGCCTGG CATGGATGGC
 CCCAAGGTGA AGCAGTGGCC CCTGACTGAG GAGAAGATCA AGGCCCTGGT GGAAATCTGC
 ACTGAGATGG AGAAGGAGGG CAAAATCTCC AAGATTGGCC CCGAGAACCC CTACAACACC
 CCTGTGTTTG CCATCAAGAA GAAGGACTCC ACCAAGTGA GGAAGCTGGT GGACTTCAGG
 GAGCTGAACA AGAGGACCCA GGACTTCTGG GAGGTGCAGC TGGGCATCCC CCACCCCGCT
 GGCCTGAAGA AGAAGAAGTC TGTGACTGTG CTGGCTGTGG GGGATGCCTA CTTCTCTGTG
 CCCCTGGATG AGGACTTCAG GAAGTACACT GCCTTCACCA TCCCCTCCAT CAACAATGAG
 ACCCTGGCA TCAGGTACCA GTACAATGTG CTGCCCCAGG GCTGGAAGGG CTCCTTGCC
 ATCTTCCAGT CCTCCATGAC CAAGATCCTG GAGCCCTTCA GGAAGCAGAA CCCTGACATT
 GTGATCTACC AGTACATGGC TGCCCTGTAT GTGGGCTCTG ACCTGGAGAT TGGGCAGCAC
 AGGACCAAGA TTGAGGAGCT GAGGCAGCAC CTGCTGAGGT GGGGCCTGAC CACCCCTGAC
 AAGAAGCACC AGAAGGAGCC CCCCTTCTG TGGATGGGCT ATGAGCTGCA CCCCACAAG
 TGGACTGTGC AGCCCATTTG GCTGCCTGAG AAGGACTCCT GGACTGTGAA TGACATCCAG
 AAGCTGGTGG GCAAGCTGAA CTGGGCCTCC CAAATCTACC CTGGCATCAA GGTGAGGCAG
 CTGTGCAAGC TGCTGAGGGG CACCAAGGCC CTGACTGAGG TGATCCCCCT GACTGAGGAG
 GCTGAGCTGG AGCTGGCTGA GAACAGGGAG ATCTGAAGG AGCCTGTGCA TGGGGTGTAC

FIGURE 33B

TATGACCCCT CCAAGGACCT GATTGCTGAG ATCCAGAAGC AGGGCCAGGG CCAGTGGACC
TACCAAATCT ACCAGGAGCC CTTCAAGAAC CTGAAGACTG GCAAGTATGC CAGGATGAGG
GGGGCCACA CCAATGATGT GAAGCAGCTG ACTGAGGCTG TGCAGAAGAT CACCACTGAG
TCCATTGTGA TCTGGGGCAA GACCCCAAG TTCAAGCTGC CCATCCAGAA GGAGACCTGG
GAGACCTGGT GGACTGAGTA CTGGCAGGCC ACCTGGATCC CTGAGTGGGA GTTTGTGAAC
ACCCCCCCC TGGTGAAGCT GTGGTACCAG CTGGAGAAGG AGCCCATTTGT GGGGGCTGAG
ACCTTCTATG TGGCTGGGGC TGCCAACAGG GAGACCAAGC TGGGCAAGGC TGGCTATGTG
ACCAACAGGG GCAGGCAGAA GGTGGTGACC CTGACTGACA CCACCAACCA GAAGACTGCC
CTCCAGGCCA TCTACCTGGC CCTCCAGGAC TCTGGCCTGG AGGTGAACAT TGTGACTGCC
TCCCAGTATG CCCTGGGCAT CATCCAGGCC CAGCCTGATC AGTCTGAGTC TGAGCTGGTG
AACCAGATCA TTGAGCAGCT GATCAAGAAG GAGAAGGTGT ACCTGGCCTG GGTGCCTGCC
CACAAGGGCA TTGGGGGCAA TGAGCAGGTG GACAAGCTGG TGTCTGCTGG CATCAGGAAG
GTGCTGTTCC TGGATGGCAT TGACAAGGCC CAGGATGAGC ATGAGAAGTA CCACTCCAAC
TGGAGGGCTA TGGCCTCTGA CTTCAACCTG CCCCTGTGG TGGCTAAGGA GATTGTGGCC
TCCTGTGACA AGTGCCAGCT GAAGGGGGAG GCCATGCATG GGCAGGTGGA CTGCTCCCTT
GGCATCTGGC AGCTGGCCTG CACCCACCTG GAGGGCAAGG TGATCCTGGT GGCTGTGCAT
GTGGCCTCCG GCTACATTGA GGCTGAGGTG ATCCCTGCTG AGACAGGCCA GGAGACTGCC
TACTTCCTGC TGAAGCTGGC TGGCAGGTGG CCTGTGAAGA CCATCCACAC TGCCAATGGC
TCCAATTCA CTGGGGCCAC AGTGAGGGCT GCCTGCTGGT GGGCTGGCAT CAAGCAGGAG
TTTCTTCC CCTACAACCC CCAGTCCCAG GGGGTGGTGG CCTCCATGAA CAAGGAGCTG
AAGAAGATCA TTGGGCAGGT GAGGGACCAG GCTGAGCACC TGAAGACAGC TGTGCAGATG
GCTGTGTTCA TCCACAACCT CAAGAGGAAG GGGGGCATCG GGGGCTACTC CGCTGGGGAG
AGGATTGTGG ACATCATTGC CACAGACATC CAGACCAAGG AGCTCCAGAA GCAGATCACC
AAGATCCAGA ACTTCAGGGT GTACTACAGG GACTCCAGGA ACCCCCTGTG GAAGGGCCCT
GCCAAGCTGC TGTGGAAGGG GGAGGGGGCT GTGGTGATCC AGGACAACCTC TGACATCAAG
GTGGTGCCCA GGAGGAAGGC CAAGATCATC AGGGACTATG GCAAGCAGAT GGCTGGGGAT
GACTGTGTGG CCTCCAGGCA GGATGAGGAC TAA
SEQ ID NO: 38

FIGURE 34A

Met Gly Ala Arg Ala Ser Val Leu Ser Gly Gly Glu Leu Asp Lys Trp Glu Lys
 Ile Arg Leu Arg Pro Gly Gly Lys Lys Lys Tyr Lys Leu Lys His Ile Val Trp
 Ala Ser Arg Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser
 Glu Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly Ser
 Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys Val His Gln
 Lys Ile Asp Val Lys Asp Thr Lys Glu Ala Leu Glu Lys Ile Glu Glu Glu Gln
 Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala Ala Gly Thr Gly Asn Ser Ser
 Gln Val Ser Gln Asn Tyr Pro Ile Val Gln Asn Leu Gln Gly Gln Met Val His
 Gln Ala Ile Ser Pro Arg Thr Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys
 Ala Phe Ser Pro Glu Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr
 Pro Gln Asp Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met
 Gln Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Leu His
 Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro Arg Gly Ser
 Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile Gly Trp Met Thr Asn
 Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys Arg Trp Ile Ile Leu Gly Leu
 Asn Lys Ile Val Arg Met Tyr Ser Pro Thr Ser Ile Leu Asp Ile Arg Gln Gly
 Pro Lys Glu Pro Phe Arg Asp Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala
 Glu Gln Ala Ser Gln Glu Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln
 Asn Ala Asn Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr
 Leu Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys Ala
 Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Ser Ala Thr Ile Met Met
 Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Thr Val Lys Cys Phe Asn Cys Gly
 Lys Val Gly His Ile Ala Lys Asn Cys Arg Ala Pro Arg Lys Lys Gly Cys Trp
 Lys Cys Gly Lys Glu Gly His Gln Met Lys Asp Cys Asn Glu Arg Gln Ala Asn
 Phe Leu Gly Lys Ile Trp Pro Ser His Lys Gly Arg Pro Gly Asn Phe Leu Gln
 Ser Arg Pro Glu Pro Thr Ala Pro Pro Glu Glu Ser Phe Arg Phe Gly Glu Glu
 Lys Thr Thr Pro Ser Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu
 Ala Ser Leu Arg Ser Leu Phe Gly Asn Asp Pro Ser Ser Gln Met Ala Pro Ile
 Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys
 Val Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile Cys
 Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr
 Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu
 Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu
 Gly Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Ala
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr
 Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr
 Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met
 Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr Gln
 Tyr Met Ala Ala Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr
 Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp
 Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro

FIGURE 34B

Asp Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro
Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr
Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu
Ile Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu Ile
Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu
Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr
Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile
Val Ile Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe
Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile
Val Gly Ala Glu Thr Phe Tyr Val Ala Gly Ala Ala Asn Arg Glu Thr Lys Leu
Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu Thr
Asp Thr Thr Asn Gln Lys Thr Ala Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp
Ser Gly Leu Glu Val Asn Ile Val Thr Ala Ser Gln Tyr Ala Leu Gly Ile Ile
Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln
Leu Ile Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu
Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn
Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile
Val Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln Val
Asp Cys Ser Pro Gly Ile Trp Gln Leu Ala Cys Thr His Leu Glu Gly Lys Val
Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro
Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp
Pro Val Lys Thr Ile His Thr Ala Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn
Pro Gln Ser Gln Gly Val Val Ala Ser Met Asn Lys Glu Leu Lys Lys Ile Ile
Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val
Phe Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly Glu
Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln
Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu
Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln
Asp Asn Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp
SEQ ID NO: 39

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- (72) Inventors; and
- (75) Inventors/Applicants (for US only): EMINI, Emilio, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). YOUIL, Rima [AU/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). BETT, Andrew, J. [CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). CHEN, Ling [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). KASLOW, David, C. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). SHIVER, John, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). TONER, Timothy, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). CASIMIRO, Daniel, R. [PH/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING CODON OPTIMIZED HIV-1 GAG, POL, NEF AND MODIFICATIONS

(57) Abstract: First generation adenoviral vectors and associated recombinant adenovirus-based HIV vaccines which show enhanced stability and growth properties and greater cellular-mediated immunity are described within this specification. These adenoviral vectors are utilized to generate and produce through cell culture various adenoviral-based HIV-1 vaccines which contain HIV-1 gag, HIV-1 pol and/or HIV-1 nef polynucleotide pharmaceutical products, and biologically relevant modifications thereof. These adenovirus vaccines, when directly introduced into living vertebrate tissue, preferably a mammalian host such as a human or a non-human mammal of commercial or domestic veterinary importance, express the HIV-1-Gag, Pol and/or Nef protein or biologically modification thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding HIV-1 Gag, encoding codon optimized HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The adenoviral vaccines of the present invention, when administered alone or in a combined modality regime, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

WO 02/22080 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/86

US CL : 435/456

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/205.1, 207.1, 227.1, 233.1; 435/69.1, 69.3, 173.3, 235.1, 320.1, 456; 530/23.72;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 96/39178 (ERTL et al.) 12 December 1996 (12.12.1996), see page 5, 6, 10, 12, 13 and claims 1 and 5.	1-3, 8-11, 18 ----- 4, 5, 13-17, 29, 30, 32, 34, 35, 37
X --- Y	US 6,019,978 A (ERTL et al.) 1 February 2000 (01/02/2000), see columns 2, 7 and 8.	1-3, 8-11, 18 ----- 4, 5, 13-17, 29, 30, 32, 34, 35, 37
X,P	US 6,287,571 A A (ERTL et al.) 11 September 2001 (11/09/2001), see columns 2, 7, 8 and claim 1.	1, 9, 18
X --- Y	US 5,643,579A (HUNG et al.) 1 July 1997 (01/07/1997), see examples 1, 2, 25 and 26.	1-3, 8, 9-11, 18 ----- 4,5,13-17, 29, 30, 32, 34, 35, 37
Y	WANG et al. The use of an E1-deleted, replication -defective adenovirus recombinant expressing the rabies virus glycoprotein for early vaccination of mice against rabies virus. Journal of Virology (March 1997) Vol. 71, No. 5, pp 3677-3683.	1-3, 9-11, 13-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"A"

document member of the same patent family

Date of the actual completion of the international search

06 February 2002 (06.02.2002)

Date of mailing of the international search report

13 MAR 2002

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Ulrike Winkler, Ph.D.

Telephone No. 703-308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NATUK et al. Immunogenicity of recombinant human adenovirus -human immunodeficiency virus vaccines in chimpanzees. Aids Research and Human Retroviruses (1993) Vol. 9, No. 5, pp395-404, see material and methods.	1, 9, 29, 30, 32
Y	PREVEC et al. Immune response to HIV-1 gag antigens induced by recombinant adenovirus vectors in mice and rhesus macaque monkeys. Journal of Acquired Immune Deficiency Syndrome. (1991) Vol. 4, No. 6 pp. 568-76, see abstract.	1, 9, 29, 30, 32
Y	LORI et al. Rapid protection against human immunodeficiency virus type 1 (HIV-1) replication mediated by high efficiency non-retroviral delivery of genes interfering with HIV-1 tat and gag. Gene Therapy (1994) Vol. 1, No. 1, pp. 27-31, see abstract.	1, 9
Y	PFARR et al. Differential effects of polyadenylation regions on gene expression in mammalian cells. DNA (1986) Vol. 5, No. 2, pp. 115-22, see abstract.	16
Y	NATUK et al. Adenovirus vectored vaccine. Developmental Biological Standards (1994) Vol. 82, pp. 71-77, see abstract.	1, 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 31
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
This claim could not be searched because applicant did not provide a CRF.
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all ⁷searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5, 8-11, 13-18, 29-32, 34, 35, 37

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

The special technical feature of group 4, 16 and 31 is considered to be a method of producing recombinant adenoviral particles. Each group contains different sequences hence the resulting particles would have different structures and functions associated with the particle.

The special technical feature of group 5, 17 and 32 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors. Each group contains different sequences encoding different protein, therefore the resulting immune response will also be different.

The special technical feature of group 6, 18 and 33 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors in conjunction with immunizing the individual a DNA plasmid vaccine. Each method contains different sequences encoding a different protein, therefore the resulting immune response will also be different.

Accordingly, groups 1-48 are not so linked by the same or corresponding technical feature as to form a single general inventive concept.

Continuation of B. FIELDS SEARCHED Item 3:

WEST 2.0, STN-BIOSIS, MEDLINE

adenoviral vector, deletion, HIV, Gag, polyadenylation signal, CMV promoter

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

		and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 1) inserted in E1.
14	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 5) inserted in E1.
15	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 7) inserted in E1.
16	57-61	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Pol protein.
17	62, 65, 66	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle.
18	63, 64	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle in addition to administering a DNA plasmid vaccine.
19	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the parallel orientation of E1.
20	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the parallel orientation of E1.
21	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the parallel orientation of E1.
22	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the parallel orientation of E1.
23	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the antiparallel orientation of E1.
24	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the antiparallel orientation of E1.
25	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the antiparallel orientation of E1.
26	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the antiparallel orientation of E1.
27	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in E1.
28	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in E1.
29	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

		and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 1) inserted in E1.
14	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 5) inserted in E1.
15	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 7) inserted in E1.
16	57-61	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Pol protein.
17	62, 65, 66	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle.
18	63, 64	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle in addition to administering a DNA plasmid vaccine.
19	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the parallel orientation of E1.
20	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the parallel orientation of E1.
21	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the parallel orientation of E1.
22	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the parallel orientation of E1.
23	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the antiparallel orientation of E1.
24	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the antiparallel orientation of E1.
25	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the antiparallel orientation of E1.
26	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the antiparallel orientation of E1.
27	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in E1.
28	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in E1.
29	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

		adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in E1.
30	74	The claim is directed to an adenoviral vector that is at least partially deleted of <u>$\Delta E1$</u> and <u>$\Delta E3$</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in E1.
31	76-80	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Nef protein.
32	81, 84, 85	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle.
33	82, 83	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle <u>in addition to administering a DNA plasmid vaccine.</u>
34	86a	The claim is drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from three individual vectors.
35	86b, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from one individual vectors.
36	86c, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-pol</i> fusion and one expressing <i>gag</i> .
37	86d, 87, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>gag-pol</i> fusion and one expressing <i>nef</i> .
38	86e, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-gag</i> fusion and one expressing <i>pol</i> .
39	86f, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from a single vectors as a fusion protein.
40	86g, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed from two individual vectors.
41	86h, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed individually from one vector.
42	86i, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from two individual vectors.
43	86j, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from individually from one vector.
44	86k, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
45	86l, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
46	86m, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed as a fusion protein from one vector.
47	86n, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed as a fusion protein from one vector.
48	86o, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed as a fusion protein from one vector.

The inventions listed as Groups 1-48 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups 1-33 appears to be a recombinant adenoviral vector wherein the adenoviral vector is at least partially deleted in E1 but the vector may contain more deletions, the vector contains wild type sequences including packaging signals and a gene encoding a heterologous HIV protein or fragments thereof. Ertl et al. (WO 96/39178) disclose a recombinant adenoviral vector that is deleted in E1 and partially deleted in E3, the remainder of the adenoviral vector contains wild type sequences. The vector additionally contains an insertion of a heterologous protein which includes HIV proteins (see abstract and claims 1 and 5). Therefore, the technical feature linking the inventions of groups 1-45 does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of the following groups 1-3, 7-15, 19-30 and 34-48 is considered to be the combination of sequences that is disclosed in each group, see individual claim groupings above for the different sequences. The DNA disclosed in each group is made up of a different sequence having a different structure and different function.

REVISED VERSION

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International Bureau(43) International Publication Date
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- (25) Filing Language: English
- (26) Publication Language: English
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60/233,180 15 September 2000 (15.09.2000) US
- (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (72) Inventors; and
(73) Inventors/Applicants (for US only): EMINI, Emilio, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). YOUIL, Rima [AU/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). BETT, Andrew, J. [CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). CHEN, Ling [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). KASLOW, David, C. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). SHIVER, John, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). TONER, Timothy, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). CASIMIRO, Daniel, R. [PH/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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see PCT Gazette No. 30/2002 of 25 July 2002, Section II
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING CODON OPTIMIZED HIV1-GAG, POL, NEF AND MODIFICATIONS

(57) Abstract: First generation adenoviral vectors and associated recombinant adenovirus-based HIV vaccines which show enhanced stability and growth properties and greater cellular-mediated immunity are described within this specification. These adenoviral vectors are utilized to generate and produce through cell culture various adenoviral-based HIV-1 vaccines which contain HIV-1 gag, HIV-1 pol and/or HIV-1 nef polynucleotide pharmaceutical products, and biologically relevant modifications thereof. These adenovirus vaccines, when directly introduced into living vertebrate tissue, preferably a mammalian host such as a human or a non-human mammal of commercial or domestic veterinary importance, express the HIV1 - Gag, Pol and/or Nef protein or biologically modification thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding HIV-1 Gag, encoding codon optimized HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The adenoviral vaccines of the present invention, when administered alone or in a combined modality regime, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/86

US CL : 435/456

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/205.1, 207.1, 227.1, 233.1; 435/69.1, 69.3, 173.3, 235.1, 320.1, 456; 530/23.72;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X — Y	WO 96/39178 (ERTL et al.) 12 December 1996 (12.12.1996), see page 5, 6, 10, 12, 13 and claims 1 and 5.	1-3, 8-11, 18 — 4, 5, 13-17, 29-32, 34, 35, 37
X — Y	US 6,019,978 A (ERTL et al.) 1 February 2000 (01/02/2000), see columns 2, 7 and 8.	1-3, 8-11, 18 — 4, 5, 13-17, 29-32, 34, 35, 37
X,P	US 6,287,571 <i>B1</i> (ERTL et al.) 11 September 2001 (11/09/2001), see columns 2, 7, 8 and claim 1.	1, 9, 18
X — Y	US 5,643,579A (HUNG et al.) 1 July 1997 (01/07/1997), see examples 1, 2, 25 and 26.	1-3, 8, 9-11, 18 — 4, 5, 13-17, 29-32, 34, 35, 37
Y	WANG et al. The use of an E1-deleted, replication-defective adenovirus recombinant expressing the rabies virus glycoprotein for early vaccination of mice against rabies virus. Journal of Virology (March 1997) Vol. 71, No. 5, pp 3677-3683.	1-3, 9-11, 13-18

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

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Date of mailing of the international search report

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Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Ulrike Winkler, Ph.D.

Telephone No. 703-308-0196

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PCT/US01/28861

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NATUK et al. Immunogenicity of recombinant human adenovirus -human immunodeficiency virus vaccines in chimpanzees. Aids Research and Human Retroviruses (1993) Vol. 9, No. 5, pp395-404, see material and methods.	1, 9, 29-32
Y	PREVEC et al. Immune response to HIV-1 gag antigens induced by recombinant adenovirus vectors in mice and rhesus macaque monkeys. Journal of Acquired Immune Deficiency Syndrome. (1991) Vol. 4, No. 6 pp. 568-76, see abstract.	1, 9, 29-32
Y	LORI et al. Rapid protection against human immunodeficiency virus type 1 (HIV-1) replication mediated by high efficiency non-retroviral delivery of genes interfering with HIV-1 tat and gag. Gene Therapy (1994) Vol. 1, No. 1, pp. 27-31, see abstract.	1, 9
Y	PFARR et al. Differential effects of polyadenylation regions on gene expression in mammalian cells. DNA (1986) Vol. 5, No. 2, pp. 115-22, see abstract.	16
Y	NATUK et al. Adenovirus vectored vaccine. Developmental Biological Standards (1994) Vol. 82, pp. 71-77, see abstract.	1, 9

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5, 8-11, 13-18, 29-32, 34, 35, 37

Remark on Protest

☐
☐

- The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group	Claims	
1	1-5, 8-11, 13-18, 29, 30, 31, 32, 34, 35, 37	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Gag protein (SEQ ID NO: 29)</u> inserted in the <u>parallel orientation</u> of E1. In addition the vector contains a promoter and a polyadenylation signal.
2	6, 7, 36	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1 and ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Gag protein (SEQ ID NO: 29).
3	12, 33	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV protein inserted in the <u>antiparallel orientation</u> of E1.
4	19-23, 38-42	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Gag protein.
5	24, 27, 28, 43, 46, 47	The claim is directed to a method of generating a cellular mediated immune response to HIV Gag protein with the recombinant adenoviral particle.
6	25, 26, 44, 45	The claim is directed to a method of generating a cellular mediated immune response to HIV Gag protein with the recombinant adenoviral particle <u>in addition to administering a DNA plasmid vaccine</u> .
7	48-51, 53, 54, 56	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 1)</u> inserted in the <u>parallel orientation</u> of E1.
8	48-51, 53, 54, 56	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 5)</u> inserted in the <u>parallel orientation</u> of E1.
9	48-51, 53, 54, 56	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 7)</u> inserted in the <u>parallel orientation</u> of E1.
10	52	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 1)</u> inserted in the <u>antiparallel orientation</u> of E1.
11	52	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 5)</u> inserted in the <u>antiparallel orientation</u> of E1.
12	52	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 7)</u> inserted in the <u>antiparallel orientation</u> of E1.
13	55	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u>

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		and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 1) inserted in E1.</u>
14	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 5) inserted in E1.</u>
15	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 7) inserted in E1.</u>
16	57-61	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an <u>HIV Pol protein.</u>
17	62, 65, 66	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle.
18	63, 64	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle <u>in addition to administering a DNA plasmid vaccine.</u>
19	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 9) inserted in the parallel orientation of E1.</u>
20	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 11) inserted in the parallel orientation of E1.</u>
21	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 13) inserted in the parallel orientation of E1.</u>
22	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 15) inserted in the parallel orientation of E1.</u>
23	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 9) inserted in the antiparallel orientation of E1.</u>
24	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 11) inserted in the antiparallel orientation of E1.</u>
25	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 13) inserted in the antiparallel orientation of E1.</u>
26	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 15) inserted in the antiparallel orientation of E1.</u>
27	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 9) inserted in E1.</u>
28	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 11) inserted in E1.</u>
29	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type

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		adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in E1.
30	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in E1.
31	76-80	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Nef protein.
32	81, 84, 85	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle.
33	82, 83	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle <u>in addition to</u> administering a DNA plasmid vaccine.
34	86a	The claim is drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from three individual vectors.
35	86b, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from one individual vectors.
36	86c, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-pol</i> fusion and one expressing <i>gag</i> .
37	86d, 87, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>gag-pol</i> fusion and one expressing <i>nef</i> .
38	86e, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-gag</i> fusion and one expressing <i>pol</i> .
39	86f, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from a single vectors as a fusion protein.
40	86g, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed from two individual vectors.
41	86h, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed individually from one vector.
42	86i, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from two individual vectors.
43	86j, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from individually from one vector.
44	86k, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
45	86l, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
46	86m, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed as a fusion protein from one vector.
47	86n, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed as a fusion protein from one vector.
48	86o, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed as a fusion protein from one vector.

The inventions listed as Groups 1-48 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups 1-33 appears to be a recombinant adenoviral vector wherein the adenoviral vector is at least partially deleted in E1 but the vector may contain more deletions, the vector contains wild type sequences including packaging signals and a gene encoding a heterologous HIV protein or fragments thereof. Erdi et al. (WO 96/39178) disclose a recombinant adenoviral vector that is deleted in E1 and partially deleted in E3, the remainder of the adenoviral vector contains wild type sequences. The vector additionally contains an insertion of a heterologous protein which includes HIV proteins (see abstract and claims 1 and 5). Therefore, the technical feature linking the inventions of groups 1-45 does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of the following groups 1-3, 7-15, 19-30 and 34-48 is considered to be the combination of sequences that is disclosed in each group, see individual claim groupings above for the different sequences. The DNA disclosed in each group is made up of a different sequence having a different structure and different function.

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The special technical feature of group 4, 16 and 31 is considered to be a method of producing recombinant adenoviral particles. Each group contains different sequences hence the resulting particles would have different structures and functions associated with the particle.

The special technical feature of group 5, 17 and 32 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors. Each group contains different sequences encoding different protein, therefore the resulting immune response will also be different.

The special technical feature of group 6, 18 and 33 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors in conjunction with immunizing the individual a DNA plasmid vaccine. Each method contains different sequences encoding a different protein, therefore the resulting immune response will also be different.

Accordingly, groups 1-48 are not so linked by the same or corresponding technical feature as to form a single general inventive concept.

Continuation of B. FIELDS SEARCHED Item 3:

WEST 2.0, STN-BIOSIS, MEDLINE

adenoviral vector, deletion, HIV, Gag, polyadenylation signal, CMV promoter

CORRECTED VERSION

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& CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway,
NJ 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): EMINI, Emilio, A.
[US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-
0907 (US). YOUIL, Rima [AU/US]; 126 East Lincoln Av-
enue, Rahway, NJ 07065-0907 (US). BETT, Andrew, J.
[CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-
0907 (US). CHEN, Ling [US/US]; 126 East Lincoln Av-
enue, Rahway, NJ 07065-0907 (US). KASLOW, David,
C. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-
0907 (US). SHIVER, John, W. [US/US]; 126 East Lincoln
Avenue, Rahway, NJ 07065-0907 (US). TONER, Timo-
thy, J. [US/US]; 126 East Lincoln Avenue, Rahway, NJ
07065-0907 (US). CASIMIRO, Daniel, R. [PH/US]; 126
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[Continued on next page]

(54) Title: ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING CODON OPTIMIZED HIV1-GAG,
POL, NEF AND MODIFICATIONS

(57) Abstract: First generation adenoviral vectors and associated recombinant adenovirus-based HIV vaccines which show enhanced stability and growth properties and greater cellular-mediated immunity are described within this specification. These adenoviral vectors are utilized to generate and produce through cell culture various adenoviral-based HIV-1 vaccines which contain HIV-1 gag, HIV-1 pol and/or HIV-1 nef polynucleotide pharmaceutical products, and biologically relevant modifications thereof. These adenovirus vaccines, when directly introduced into living vertebrate tissue, preferably a mammalian host such as a human or a non-human mammal of commercial or domestic veterinary importance, express the HIV-1 Gag, Pol and/or Nef protein or biologically modification thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding HIV-1 Gag, encoding codon optimized HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The adenoviral vaccines of the present invention, when administered alone or in a combined modality regime, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

WO 02/022080 A3



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE OF THE INVENTION
ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING
CODON OPTIMIZED HIV1-GAG, POL, NEF AND MODIFICATIONS

5 CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit, under 35 U.S.C. §119(e), of U.S. provisional applications 60/233,180, 60/279,056, and Attorney Docket 20867PV2 (serial number unassigned), filed September 15, 2000, March 27, 2001, and September 7, 2001, respectively.

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STATEMENT REGARDING FEDERALLY-SPONSORED R&D

Not Applicable

REFERENCE TO MICROFICHE APPENDIX

15

Not Applicable

FIELD OF THE INVENTION

The present invention relates to recombinant, replication-deficient first generation adenovirus vaccines found to exhibit enhanced growth properties and greater cellular-mediated immunity as compared to other replication-deficient vectors. The invention also relates to the associated first generation adenoviral vectors described herein, which, through the incorporation of additional 5' adenovirus sequence, enhance large scale production efficiency of the recombinant, replication-defective adenovirus described herein. Another aspect of the instant invention is the surprising discovery that the intron A portion of the human cytomegalovirus (hCMV) promoter constitutes a region of instability in adenoviral vector constructs. Removal of this region from adenoviral-expression constructs results in greatly improved vector stability. Therefore, improved vectors expressing a transgene under the control of an intron A-deleted CMV promoter constitute a further aspect of this invention. These adenoviral vectors are useful for generating recombinant adenovirus vaccines against human immunodeficiency virus (HIV). In particular, the first generation adenovirus vectors disclosed herein are utilized to construct and generate adenovirus-based HIV-1 vaccines which contain HIV-1 Gag, HIV-1 Pol and/or HIV-1 Nef polynucleotide pharmaceutical products, and biologically active modifications thereof. Host administration of the recombinant, replication-deficient adenovirus vaccines described herein results in expression of HIV-1 Gag, HIV-1 Pol and/or Nef protein or

immunologically relevant modifications thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding codon optimized HIV-1 Gag, HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef, and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The HIV adenovirus vaccines of the present invention, when administered alone or in a combined modality and/or prime/boost regimen, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

BACKGROUND OF THE INVENTION

Human Immunodeficiency Virus-1 (HIV-1) is the etiological agent of acquired human immune deficiency syndrome (AIDS) and related disorders. HIV-1 is an RNA virus of the Retroviridae family and exhibits the 5' LTR-*gag-pol-env*-LTR 3' organization of all retroviruses. The integrated form of HIV-1, known as the provirus, is approximately 9.8 Kb in length. Each end of the viral genome contains flanking sequences known as long terminal repeats (LTRs). The HIV genes encode at least nine proteins and are divided into three classes; the major structural proteins (Gag, Pol, and Env), the regulatory proteins (Tat and Rev); and the accessory proteins (Vpu, Vpr, Vif and Nef).

The *gag* gene encodes a 55-kilodalton (kDa) precursor protein (p55) which is expressed from the unspliced viral mRNA and is proteolytically processed by the HIV protease, a product of the *pol* gene. The mature p55 protein products are p17 (matrix), p24 (capsid), p9 (nucleocapsid) and p6.

The *pol* gene encodes proteins necessary for virus replication; a reverse transcriptase, a protease, integrase and RNase H. These viral proteins are expressed as a Gag-Pol fusion protein, a 160 kDa precursor protein which is generated via a ribosomal frame shifting. The viral encoded protease proteolytically cleaves the Pol polypeptide away from the Gag-Pol fusion and further cleaves the Pol polypeptide to the mature proteins which provide protease (Pro, P10), reverse transcriptase (RT, P50), integrase (IN, p31) and RNase H (RNase, p15) activities.

The *nef* gene encodes an early accessory HIV protein (Nef) which has been shown to possess several activities such as down regulating CD4 expression, disturbing T-cell activation and stimulating HIV infectivity.

5 The *env* gene encodes the viral envelope glycoprotein that is translated as a 160-kilodalton (kDa) precursor (gp160) and then cleaved by a cellular protease to yield the external 120-kDa envelope glycoprotein (gp120) and the transmembrane 41-kDa envelope glycoprotein (gp41). Gp120 and gp41 remain associated and are displayed on the viral particles and the surface of HIV-infected cells.

10 The *tat* gene encodes a long form and a short form of the Tat protein, a RNA binding protein which is a transcriptional transactivator essential for HIV-1 replication.

The *rev* gene encodes the 13 kDa Rev protein, a RNA binding protein. The Rev protein binds to a region of the viral RNA termed the Rev response element (RRE). The Rev protein promotes transfer of unspliced viral RNA from the nucleus
15 to the cytoplasm. The Rev protein is required for HIV late gene expression and in turn, HIV replication.

Gp120 binds to the CD4/chemokine receptor present on the surface of helper T-lymphocytes, macrophages and other target cells in addition to other co-receptor molecules. X4 (macrophage tropic) virus show tropism for CD4/CXCR4 complexes
20 while a R5 (T-cell line tropic) virus interacts with a CD4/CCR5 receptor complex. After gp120 binds to CD4, gp41 mediates the fusion event responsible for virus entry. The virus fuses with and enters the target cell, followed by reverse transcription of its single stranded RNA genome into the double-stranded DNA via a RNA dependent DNA polymerase. The viral DNA, known as provirus, enters the cell nucleus, where
25 the viral DNA directs the production of new viral RNA within the nucleus, expression of early and late HIV viral proteins, and subsequently the production and cellular release of new virus particles. Recent advances in the ability to detect viral load within the host shows that the primary infection results in an extremely high generation and tissue distribution of the virus, followed by a steady state level of virus
30 (albeit through a continual viral production and turnover during this phase), leading ultimately to another burst of virus load which leads to the onset of clinical AIDS. Productively infected cells have a half life of several days, whereas chronically or latently infected cells have a 3-week half life, followed by non-productively infected cells which have a long half life (over 100 days) but do not significantly contribute to
35 day to day viral loads seen throughout the course of disease.

Destruction of CD4 helper T lymphocytes, which are critical to immune defense, is a major cause of the progressive immune dysfunction that is the hallmark of HIV infection. The loss of CD4 T-cells seriously impairs the body's ability to fight most invaders, but it has a particularly severe impact on the defenses against viruses, fungi, parasites and certain bacteria, including mycobacteria.

Effective treatment regimens for HIV-1 infected individuals have become available recently. However, these drugs will not have a significant impact on the disease in many parts of the world and they will have a minimal impact in halting the spread of infection within the human population. As is true of many other infectious diseases, a significant epidemiologic impact on the spread of HIV-1 infection will only occur subsequent to the development and introduction of an effective vaccine. There are a number of factors that have contributed to the lack of successful vaccine development to date. As noted above, it is now apparent that in a chronically infected person there exists constant virus production in spite of the presence of anti-HIV-1 humoral and cellular immune responses and destruction of virally infected cells. As in the case of other infectious diseases, the outcome of disease is the result of a balance between the kinetics and the magnitude of the immune response and the pathogen replicative rate and accessibility to the immune response. Pre-existing immunity may be more successful with an acute infection than an evolving immune response can be with an established infection. A second factor is the considerable genetic variability of the virus. Although anti-HIV-1 antibodies exist that can neutralize HIV-1 infectivity in cell culture, these antibodies are generally virus isolate-specific in their activity. It has proven impossible to define serological groupings of HIV-1 using traditional methods. Rather, the virus seems to define a serological "continuum" so that individual neutralizing antibody responses, at best, are effective against only a handful of viral variants. Given this latter observation, it would be useful to identify immunogens and related delivery technologies that are likely to elicit anti-HIV-1 cellular immune responses. It is known that in order to generate CTL responses antigen must be synthesized within or introduced into cells, subsequently processed into small peptides by the proteasome complex, and translocated into the endoplasmic reticulum/Golgi complex secretory pathway for eventual association with major histocompatibility complex (MHC) class I proteins. CD8⁺ T lymphocytes recognize antigen in association with class I MHC via the T cell receptor (TCR) and the CD8 cell surface protein. Activation of naive CD8⁺ T cells into activated effector or memory cells generally requires both TCR engagement of antigen as described above as well as engagement of costimulatory proteins. Optimal

induction of CTL responses usually requires "help" in the form of cytokines from CD4⁺ T lymphocytes which recognize antigen associated with MHC class II molecules via TCR and CD4 engagement.

European Patent Applications 0 638 316 (Published February 15, 1995) and 0 586 076 (Published March 9, 1994), (both assigned to American Home Products Corporation) describe replicating adenovirus vectors carrying an HIV gene, including *env* or *gag*. Various treatment regimens were used with chimpanzees and dogs, some of which included booster adenovirus or protein plus alum treatments.

Replication-defective adenoviral vectors harboring deletions in the E1 region are known, and recent adenoviral vectors have incorporated the known packaging repeats into these vectors; e.g., see EP 0 707 071, disclosing, *inter alia*, an adenoviral vector deleted of E1 sequences from base pairs 459 to 3328; and U.S. Patent No. 6,033,908, disclosing, *inter alia*, an adenoviral vector deleted of base pairs 459-3510. The packaging efficiency of adenovirus has been taught to depend on the number of incorporated individual A (packaging) repeats; see, e.g., Gräble and Hearing, 1990 *J. Virol.* 64(5):2047-2056; Gräble and Hearing, 1992 *J. Virol.* 66(2):723-731.

Larder, et al., (1987, *Nature* 327: 716-717) and Larder, et al., (1989, *Proc. Natl. Acad. Sci.* 86: 4803-4807) disclose site specific mutagenesis of HIV-1 RT and the effect such changes have on *in vitro* activity and infectivity related to interaction with known inhibitors of RT.

Davies, et al. (1991, *Science* 252:, 88-95) disclose the crystal structure of the RNase H domain of HIV-1 Pol.

Schatz, et al. (1989, *FEBS Lett.* 257: 311-314) disclose that mutations Glu478Gln and His539Phe in a complete HIV-1 RT/RNase H DNA fragment results in defective RNase activity without effecting RT activity.

Mizrahi, et al. (1990, *Nucl. Acids. Res.* 18: pp. 5359-5353) disclose additional mutations Asp443Asn and Asp498Asn in the RNase region of the *pol* gene which also results in defective RNase activity. The authors note that the Asp498Asn mutant was difficult to characterize due to instability of this mutant protein.

Leavitt, et al. (1993, *J. Biol. Chem.* 268: 2113-2119) disclose several mutations, including a Asp64Val mutation, which show differing effect on HIV-1 integrase (IN) activity.

Wiskerchen, et al. (1995, *J. Virol.* 69: 376-386) disclose single and double mutants, including mutation of aspartic acid residues which effect HIV-1 IN and viral replication functions.

It would be of great import in the battle against AIDS to produce a prophylactic- and/or therapeutic-based HIV vaccine which generates a strong cellular immune response against an HIV infection. The present invention addresses and meets these needs by disclosing a class of adenovirus vaccines which, upon host administration, express codon optimized and modified versions of the HIV-1 genes, *gag*, *pol* and *nef*. These recombinant, replication-defective adenovirus vaccines may be administered to a host, such as a human, alone or as part of a combined modality regimen and/or prime-boost vaccination regimen with components of the present invention and/or a distinct viral HIV DNA vaccine, non-viral HIV DNA vaccine, HIV subunit vaccine, an HIV whole killed vaccine and/or a live attenuated HIV vaccine.

SUMMARY OF THE INVENTION

The present invention relates to enhanced replication-defective recombinant adenovirus vaccine vectors and associated recombinant, replication-deficient adenovirus vaccines which encode various forms of HIV-1 Gag, HIV-1 Pol, and/or HIV-1 Nef, including immunologically relevant modifications of HIV-1 Gag, HIV-1 Pol and HIV-1 Nef. The adenovirus vaccines of the present invention express HIV antigens and provide for improved cellular-mediated immune responses upon host administration. Potential vaccinees include but are not limited to primates and especially humans and non-human primates, and also include any non-human mammal of commercial or domestic veterinary importance. An effect of the improved recombinant adenovirus-based vaccines of the present invention should be a lower transmission rate to previously uninfected individuals (i.e., prophylactic applications) and/or reduction in the levels of the viral loads within an infected individual (i.e., therapeutic applications), so as to prolong the asymptomatic phase of HIV-1 infection. In particular, the present invention relates to adenoviral-based vaccines which encode various forms of codon optimized HIV-1 Gag (including but in no way limited to p55 versions of codon optimized full length (FL) Gag and tPA-Gag fusion proteins), HIV-1 Pol, HIV-1 Nef, and selected modifications of immunological relevance. The administration, intracellular delivery and expression of these adenovirus vaccines elicit a host CTL and Th response. The preferred replication-defective recombinant adenoviral vaccine vectors include but are not limited to synthetic DNA molecules which (1) encode codon optimized versions of wild type HIV-1 Gag; (2) encode codon optimized versions of HIV-1 Pol; (3) encode codon optimized versions of HIV-1 Pol fusion proteins; (4) encode codon optimized versions of modified HIV-1 Pol proteins and fusion proteins, including but not limited

to *pol* modifications involving residues within the catalytic regions responsible for RT, RNase and IN activity within the host cell; (5) encode codon optimized versions of wild type HIV-1 Nef; (6) codon optimized versions of HIV-1 Nef fusion proteins; and/or (7) codon optimized versions of HIV-1 Nef derivatives, including but not
5 limited to *nef* modifications involving introduction of an amino-terminal leader sequence, removal of an amino-terminal myristylation site and/or introduction of dileucine motif mutations. The Nef-based fusion and modified proteins, disclosed within this specification and expressed from an adenoviral-based vector vaccine this specification, may possess altered trafficking and/or host cell function while retaining
10 the ability to be properly presented to the host MHC I complex and in turn elicit a host CTL and Th response. Examples of HIV-1 Gag, Pol and/or Nef fusion proteins include but are not limited to fusion of a leader or signal peptide at the NH₂-terminal portion of the viral antigen coding region. Such a leader peptide includes but is not limited to a tPA leader peptide.

15 The adenoviral vector utilized in construction of the HIV-1 Gag-, HIV-1 Pol- and/or HIV-1 Nef- based vaccines of the present invention may comprise any replication-defective adenoviral vector which provides for enhanced genetic stability of the recombinant adenoviral genome through large scale production and purification of the recombinant virus. In other words, an HIV-1 Gag-, Pol- or Nef-based
20 adenovirus vaccine of the present invention is a purified recombinant, replication-defective adenovirus which is shown to be genetically stable through multiple passages in cell culture and remains so during large scale production and purification procedures. Such a recombinant adenovirus vector and harvested adenovirus vaccine lends itself to large scale dose filling and subsequent worldwide distribution
25 procedures which will be demanded of an efficacious monovalent or multivalent HIV vaccine. The present invention meets this basic requirement with description of a replication-defective adenoviral vector and vectors derived therefrom, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to
30 about base pair 458 of the wildtype adenovirus genome. A preferred embodiment of the instant invention comprises base pairs 1-450 of a wildtype adenovirus. In other preferred embodiments, the replication -defective adenoviral vector has, in addition thereto, a region 3' to the E1-deleted region comprising base pairs 3511-3523. Basepairs 342-450 (more particularly, 400-450) constitute an extension of the
35 5' region of previously disclosed vectors carrying viral antigens, particularly HIV antigens (see, e.g., PCT International Application PCT/US00/18332, published

January 11, 2001 (WO 01/02067), which claims priority to U.S. Provisional Application Serial Nos. 60/142,631 and 60/148,981, filed 7/6/1999 and 8/13/1999, respectively; these documents herein incorporated by reference. Applicants have found that extending the 5' region further into the E1 gene into the disclosed vaccine
5 vectors incorporated elements found to be important in optimizing the packaging of the virus.

As compared to previous vectors not comprising basepairs from about 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 of the wildtype adenovirus genome, vectors comprising the above region exhibited enhanced
10 growth characteristics, with approximately 5-10 fold greater amplification rates, a more potent virus effect, allowing lower doses of virus to be used to generate equivalent immunity; and a greater cellular-mediated immune response than replication-deficient vectors not comprising this region (basepairs 1-450). Even more important, adenoviral constructs derived therefrom are very stable genetically in
15 large-scale production, particularly those comprising an expression cassette under the control of a hCMV promoter devoid of intron A. This is because Applicants have surprisingly found that the intron A portion of the hCMV promoter constituted a region of instability when employed in adenoviral vectors. Applicants have, therefore, identified an enhanced adenoviral vector which is particularly suited for use
20 in gene therapy and nucleotide-based vaccine vectors which, favorably, lends itself to large scale propagation.

A preferred embodiment of this invention is a replication-defective adenoviral vector in accordance with the above description wherein the gene is inserted in the form of a gene expression cassette comprising (a) a nucleic acid encoding a protein or
25 biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and, (c) a transcription terminator.

In preferred embodiments, the E1 gene, other than that contained within basepairs 1-450 or, alternatively, that contained within base pairs 1-450 and 3511-
30 3523 has been deleted from the adenoviral vector, and the gene expression cassette has replaced the deleted E1 gene. In other preferred embodiments, the replication defective adenovirus genome does not have a functional E3 gene, or the E3 gene has been deleted. Most preferably, the E3 region is present within the adenoviral genome. Further preferred embodiments are wherein the gene expression cassette is in an E1
35 anti-parallel (transcribed in a 3' to 5' direction relative to the vector backbone)

orientation or, more preferably, an E1 parallel (transcribed in a 5' to 3' direction relative to the vector backbone) orientation.

Further embodiments relate to a shuttle plasmid vector comprising: an adenoviral portion and a plasmid portion, wherein said adenovirus portion comprises:

- 5 a) a replication defective adenovirus genome, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 (preferably, 1-450) of the wildtype adenovirus genome and, preferably, in addition thereto, basepairs 3511-3523 of a wildtype adenovirus sequence; and b) a gene
10 expression cassette comprising: (a) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and (c) a transcription terminator and/or a polyadenylation site.

- Other aspects of this invention include a host cell comprising said adenoviral
15 vectors and/or said shuttle plasmid vectors; vaccine compositions comprising said vectors; and methods of producing the vectors comprising (a) introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and (b) harvesting the resultant adenoviral vectors.

- To this end, the present invention particularly relates to harvested
20 recombinant, replication defective virus derived from a host cell, such as but not limited to 293 cells or PER.C6[®] cells, including but not limited to harvested virus related to any of the MRKAd5 vector backbones, with or without an accompanying transgene, including but not limited to the HIV-1 antigens described herein. An HIV-1 vaccine is represented by any harvested, recombinant adenovirus material
25 which expresses any one or more of the HIV-1 antigens disclosed herein. This harvested material may then be purified, formulated and stored prior to host administration.

- Another aspect of this invention is a method of generating a cellular immune response against a protein in an individual comprising administering to the individual
30 an adenovirus vaccine vector comprising:

- a) a recombinant, replication defective adenoviral vector, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting adenovirus packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 (preferably, 1-450) and, preferably in addition thereto,
35 base pairs 3511-3523 of a wildtype adenovirus sequence, and,

b) a gene expression cassette comprising: (i) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (ii) a heterologous promoter operatively linked to the nucleic acid of part a); and (iii) a transcription terminator and/or a polyadenylation site.

5 In view of the efficacious nature of the adenoviral and/or DNA plasmid vaccines described herein, the present invention relates to all methodology regarding administration of one or more of these adenoviral and/or DNA plasmid vaccines to provide effective immunoprophylaxis, to prevent establishment of an HIV-1 infection following exposure to this virus, or as a post-HIV infection therapeutic vaccine to
10 mitigate the acute HIV-1 infection so as to result in the establishment of a lower virus load with beneficial long term consequences. As discussed herein, such a treatment regimen may include a monovalent or multivalent composition, various combined modality applications, and/or a prime/boost regimen to as to optimize antigen expression and a concomitant cellular-mediated and/or humoral immune response
15 upon inoculation into a living vertebrate tissue. Therefore, the present invention provides for methods of using the adenoviral and/or DNA plasmid vaccines disclosed herein within the various parameters disclosed herein as well as any additional parameters known in the art, which, upon introduction into mammalian tissue induces intracellular expression of the gag, pol and/or nef-based vaccines.

20 To this end, the present invention relates in part to methods of generating a cellular immune response in a vaccinee, preferably a human vaccinee, wherein the individual is given more than one administration of adenovirus vaccine vector, and it may be given in a regimen accompanied by the administration of a plasmid vaccine. The plasmid vaccine (also referred to herein as a "DNA plasmid vaccine" or "vaccine plasmid" comprises a nucleic acid encoding a protein or an immunologically relevant
25 portion thereof, a heterologous promoter operably linked to the nucleic acid sequence, and a transcription terminator or a polyadenylation signal (such as bGH or SPA, respectively). There may be a predetermined minimum amount of time separating the administrations. The individual can be given a first dose of plasmid vaccine, and then
30 a second dose of plasmid vaccine. Alternatively, the individual may be given a first dose of adenovirus vaccine, and then a second dose of adenovirus vaccine. In other embodiments, the plasmid vaccine is administered first, followed after a time by administration of the adenovirus vaccine. Conversely, the adenovirus vaccine may be administered first, followed by administration of plasmid vaccine after a time. In
35 these embodiments, an individual may be given multiple doses of the same adenovirus serotype in either viral vector or plasmid form, or the virus may be of

differing serotypes. In the alternative, a viral antigen of interest can be first delivered via a viral vaccine other than an adenovirus-based vaccine, and then followed with the adenoviral vaccine disclosed. Alternative viral vaccines include but are not limited to pox virus and venezuelan equine encephalitis virus.

5 The present invention also relates to multivalent adenovirus vaccine compositions which comprise Gag, Pol and Nef components described herein; see, e.g., Example 29 and Table 25. Such compositions will provide for an enhanced cellular immune response subsequent to host administration, particularly given the genetic diversity of human MHCs and of circulating virus. Examples, but not
10 limitations, include MRKAd5-vector based multivalent vaccine compositions which provide for a divalent (i.e., gag and nef, gag and pol, or pol and nef components) or a trivalent vaccine (i.e., gag, pol and nef components) composition. Such a multivalent vaccine may be filled for a single dose or may consist of multiple inoculations of each individually filled component; and may in addition be part of a prime/boost regimen
15 with viral or non-viral vector vaccines as introduced in the previous paragraph. To this end, preferred compositions are MRKAd5 adenovirus used in combination with multiple, distinct HIV antigen classes. Each HIV antigen class is subject to sequence manipulation, thus providing for a multitude of potential vaccine combinations; and such combinations are within the scope of the present invention. The utilization of
20 such combined modalities vaccine formulation and administration increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a single modality regimen.

 The concept of a "combined modality" as disclosed herein also covers the alternative mode of administration whereby multiple HIV-1 viral antigens may be
25 ligated into a proper shuttle plasmid for generation of a pre-adenoviral plasmid comprising multiple open reading frames. For example, a trivalent vector may comprise a gag-pol-nef fusion, in either a E3(-) or E3(+) background, preferably a E3 deleted backbone, or possibly a "2+1" divalent vaccine, such as a gag-pol fusion (i.e., codon optimized p55 gag and inactivated optimized pol; Example 29 and Table 25)
30 within the same MRKAd5 backbone, with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the two open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES). Therefore, a multivalent vaccine delivered as a single, or possibly a second
35 harvested recombinant, replication-deficient adenovirus is contemplated as part of the present invention.

Therefore, the adenoviral vaccines and plasmid DNA vaccines of this invention may be administered alone, or may be part of a prime and boost administration regimen. A mixed modality priming and booster inoculation scheme will result in an enhanced immune response, particularly if pre-existing anti-vector immune responses are present. This one aspect of this invention is a method of priming a subject with the plasmid vaccine by administering the plasmid vaccine at least one time, allowing a predetermined length of time to pass, and then boosting by administering the adenoviral vaccine. Multiple primings typically, 1-4, are usually employed, although more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. In experiments with rhesus monkeys, the animals were primed four times with plasmid vaccines, then were boosted 4 months later with the adenoviral vaccine. Their cellular immune response was notably higher than that of animals which had only received adenoviral vaccine. The use of a priming regimen may be particularly preferred in situations where a person has a pre-existing anti-adenovirus immune response.

It is an object of the present invention to provide for enhanced replication-defective recombinant adenoviral vaccine vector backbones. These recombinant adenoviral backbones may accept one or more transgenes, which may be passaged through cell culture for growth, amplification and harvest.

It is a further object to provide for enhanced replication-defective recombinant adenoviral vaccine vectors which encode various transgenes.

It is also an object of the present invention to provide for a harvested recombinant, replication-deficient adenovirus which shows enhanced growth and amplification rates while in combination with increased virus stability after continuous passage in cell culture. Such a recombinant adenovirus is particularly suited for use in gene therapy and nucleotide-based vaccine vectors which, favorably, lends itself to large scale propagation.

To this end, it is an object of the present invention to provide for (1) enhanced replication-defective recombinant adenoviral vaccine vectors as described herein which encode various forms of HIV-1 Gag, HIV-1 Pol, and/or HIV-1 Nef, including immunologically relevant modifications of HIV-1 Gag, HIV-1 Pol and HIV-1 Nef, and (2) harvested, purified recombinant replication-deficient adenovirus generated by passage of the adenoviral vectors of (1) through one or multiple passages through cell culture, including but not limited to passage through 293 cells or PER.C6® cells.

It is also an object of the present invention to provide for recombinant adenovirus harvested by one or multiple passages through cell culture. As relating to recombinant adenoviral vaccine vector, this recombinant virus is harvested and formulated for subsequent host administration.

5 It is also an object of the present invention to provide for replication-defective adenoviral vectors wherein at least one gene is inserted in the form of a gene expression cassette comprising (a) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and, (c) a transcription terminator.

10 It is also an object of the present invention to provide for a host cell comprising said adenoviral vectors and/or said shuttle plasmid vectors; vaccine compositions comprising said vectors; and methods of producing the vectors comprising (a) introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and (b) harvesting the resultant adenoviral vectors.

15 It is a further object of the present invention to provide for methods of generating a cellular immune response against a protein in an individual comprising administering to the individual an adenovirus vaccine vector comprising a) a replication defective adenoviral vector, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair
20 342 (more preferably, 400) to about 450 (preferably, 1-450) and, preferably, 3511-3523 of a wildtype adenovirus sequence, and, b) a gene expression cassette comprising: (i) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (ii) a heterologous promoter operatively linked to the nucleic acid of part a); and (iii) a transcription terminator and/or a
25 polyadenylation site.

 It is also an object of the present invention to provide various alternatives for vaccine administration regimes, namely administration of one or more adenoviral and/or DNA plasmid vaccines described herein to provide effective immunoprophylaxis for uninfected individuals or a therapeutic treatment for HIV
30 infected patients. Such processes include but are not limited to multivalent HIV-1 vaccine compositions, various combined modality regimes as well as various prime/boost alternatives. These methods of administration, relating to vaccine composition and/or scheduled administration, will increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a
35 single modality regimen.

As used throughout the specification and claims, the following definitions and abbreviations are used:

"HAART" refers to -- highly active antiretroviral therapy --.

"first generation" vectors are characterized as being replication-defective.

- 5 They typically have a deleted or inactivated E1 gene region, and preferably have a deleted or inactivated E3 gene region as well.

"AEX" refers to Anion Exchange chromatography.

"QPA" refers to Quick PCR-based Potency Assay.

"bps" refers to basepairs.

- 10 "s" or "str" denotes that the transgene is in the E1 parallel or "straight" orientation.

"PBMCs" refers to peripheral blood monocyte cells.

"FL" refers to full length.

"FLgag" refers to a full-length optimized gag gene, as shown in Figure 2.

- 15 "Ad5-Flgag" refers to an adenovirus serotype 5 replication deficient virus which carries an expression cassette which comprises a full length optimized gag gene under the control of a CMV promoter.

- "Promoter" means a recognition site on a DNA strand to which an RNA polymerase binds. The promoter forms an initiation complex with RNA polymerase to initiate and drive transcriptional activity. The complex can be modified by activating sequences such as enhancers or inhibiting sequences such as silencers.
- 20

"Leader" means a DNA sequence at the 5' end of a structural gene which is transcribed along with the gene. This usually results a protein having an N-terminal peptide extension, often referred to as a pro-sequences.

- 25 "Intron" means a section of DNA occurring in the middle of a gene which does not code for an amino acid in the gene product. The precursor RNA of the intron is excised and is therefore not transcribed into mRNA not translated into protein.

- "Immunologically relevant" or "biologically active" means (1) with regards to a viral protein, that the protein is capable, upon administration, of eliciting a measurable immune response within an individual sufficient to retard the propagation and/or spread of the virus and/or to reduce the viral load present within the individual; or (2) with regards to a nucleotide sequence, that the sequence is capable of encoding for a protein capable of the above.
- 30

- "Cassette" refers to a nucleic acid sequence which is to be expressed, along with its transcription and translational control sequences. By changing the cassette, a vector can express a different sequence.
- 35

"bGHpA" refers to the bovine growth hormone transcription terminator/polyadenylation sequence.

"tPAgag" refers to a fusion between the leader sequence of the tissue plasminogen activator leader sequence and an optimized HIV gag gene, as exemplified in Figure 30A-B, whether in a DNA or adenovirus-based vaccine vector.

Where utilized, "IA" or "inact" refers to an inactivated version of a gene (e.g. IApol).

"MCS" is "multiple cloning site".

In general, adenoviral constructs, gene constructs are named by reference to the genes contained therein. For example:

"Ad5 HIV-1 gag", also referred to as the original HIV-1 gag adenoviral vector, is a vector containing a transgene cassette composed of a hCMV intron A promoter, the full length version of the human codon-optimized HIV-1 gag gene, and the bovine growth hormone polyadenylation signal. The transgene was inserted in the E1 antiparallel orientation in an E1 and E3 deleted adenovector.

"MRK Ad5 HIV-1 gag" also referred to as "MRKAd5gag" or "Ad5gag2" is an adenoviral vector taught herein which is deleted of E1, comprises basepairs 1-450 and 3511-3523, and has a human codon-optimized HIV-1 gene in an E1 parallel orientation under the control of a CMV promoter without intron A. The construct also comprises a bovine growth hormone polyadenylation signal.

"pV1JnsHIVgag", also referred to as "HIVFLgagPR9901", is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone.

"pV1JnsCMV(no intron)-FLgag-bGHpA" is a plasmid derived from pV1JnsHIVgag which is deleted of the intron A portion of CMV and which comprises the full length HIV gag gene. This plasmid is also referred to as "pV1JnsHIVgag-bGHpA", pV1Jns-hCMV-FL-gag-bGHpA" and "pV1JnsCMV(no intron) + FLgag + bGHpA".

"pV1JnsCMV(no intron)-FLgag-SPA" is a plasmid of the same composition as pV1JnsCMV(no intron)-FLgag-bGHpA except that the SPA termination sequence replaces that of bGHpA. This plasmid is also referred to as "pV1Jns-HIVgag-SPA" and pV1Jns-hCMV-FLgag-SPA".

"pdelE1sp1A" is a universal shuttle vector with no expression cassette (i.e., no promoter or polyA). The vector comprises wildtype adenovirus serotype 5 (Ad5) sequences from bp 1 to bp 341 and bp 3524 to bp 5798, and has a multiple cloning

site between the Ad5 sequences ending 341 bp and beginning 3524 bp. This plasmid is also referred to as the original Ad 5 shuttle vector.

"MRKpdelE1sp1A" or "MRKpdelE1(Pac/pIX/pack450)" or "MRKpdelE1(Pac/pIX/pack450)Cla1" is a universal shuttle vector with no expression cassette (i.e. no promoter or polyA) comprising wildtype adenovirus serotype 5 (Ad5) sequences from bp1 to bp450 and bp 3511 to bp 5798. The vector has a multiple cloning site between the Ad5 sequence ending 450 bp and beginning 3511 bp. This shuttle vector may be used to insert the CMV promoter and the bGHpA fragments in both the straight ("str". or E1 parallel) orientation or in the opposite (opp. or E1 antiparallel) orientation)

"MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.)" is still another shuttle vector which is the modified vector that contains the CMV promoter (no intronA) and the bGHpA fragments. The expression unit containing the hCMV promoter (no intron A) and the bovine growth hormone polyadenylation signal has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*III site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1/E3+)Cla1 pre-plasmid. This shuttle vector, as shown in Figures 22 and 23, was used to insert the respective IAPol and G2A,LLAA nef genes directly into.

"MRKpdelE1-CMV(no intron)-FLgag-bGHpA" is a shuttle comprising Ad5 sequences from basepairs 1-450 and 3511-5798, with an expression cassette containing human CMV without intron A, the full-length human codon-optimized HIV gag gene and bovine growth hormone polyadenylation signal. This plasmid is also referred to as "MRKpdelE1 shuttle +hCMV-FL-gag-BGHpA"

"MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA" is an adenoviral vector comprising all Ad5 sequences except those nucleotides encompassing the E1 region (from 451-3510), a human CMV promoter without intron A, a full-length human codon-optimized HIV gag gene, and a bovine growth hormone polyadenylation signal. This vector is also referred to as "MRKpAdHVE3 + hCMV-FL-gag-BGHpA", "MRKpAd5HIV-1gag", "MRKpAd5gag", "pMRKAd5gag" or "pAd5gag2".

"pV1Jns-HIV-pol inact(opt)" or "pV1Jns-HIV IA pol (opt)" is the inactivated Pol gene (contained within SEQ ID NO:3) cloned into the *Bgl*II site of V1Jns (Figure 17A-C). As noted herein, various derivatives of HIV-1 pol may be cloned into a plasmid expression vector such as V1Jns or V1Jns-tPA, thus serving directly as DNA vaccine candidates or as a source for subcloning into an appropriate adenoviral vector.

"MRKpdel+hCMVmin+FL-pol+bGHpA(s)" is the "MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.)" shuttle mentioned above which contains the LA pol gene in the proper orientation. This shuttle vector is used in a bacterial recombination with MRKpAd(E1-/E3+)Cla1.

5 "MRKpAd+hCMVmin+FL-pol+bGHpA(S)E3+", also referred to herein as "pMRKAd5pol", is the pre-adenovirus plasmid which comprises a CMV-pol inact(opt)-pGHpA construct. The construction of this pre-adenovirus plasmid is shown in Figure 22.

"pV1Jns/nef (G2A,LLAA)" or "V1Jns/opt nef (G2A,LLAA)" comprises
10 codon optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175 (SEQ ID NO:13; which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662). This fragment is subcloned into the Bgl II site of V1Jns
15 and/orV1Jns-tPA (Figures 16A-B). As noted above for HIV-1 pol, HIV-1 nef constructs may be cloned into a plasmid expression vector such as V1Jns or V1Jns-tPA, thus serving directly as DNA vaccine candidates or as a source for subcloning into an appropriate adenoviral vector.

"MRKpdelE1hCMVminFL-nefBGHpA(s)", also referred to herein as
20 "pMRKAd5nef", is the pre-adenovirus plasmid which comprises a CMV-nef (G2A,LLAA) codon optimized sequence. The construction of this pre-adenovirus plasmid is shown in Figure 23.

BRIEF DESCRIPTION OF THE FIGURES

25 Figure 1 shows the original HIV-1 gag adenovector (Ad5HIV-1gag). This vector is disclosed in PCT International Application No. PCT/US00/18332 (WO 01/02607) filed July 3, 2000, claiming priority to U.S. Provisional Application Serial No. 60/142,631, filed July 6, 1999 and U.S. Application Serial No. 60/148,981, filed August 13, 1999, all three applications which are hereby incorporated by reference.

30 Figure 2 shows the nucleic acid sequence (SEQ ID NO: 29) of the optimized human HIV-1 gag open reading frame.

Figure 3 shows diagrammatically the new transgene constructs in comparison with the original gag transgene.

Figure 4 shows the modifications made to the original adenovector backbone
35 in the generation of the novel vectors of the instant invention.

Figure 5 shows the virus mixing experiments that were carried out to determine the effects of the addition made to the packaging signal region (Expt. #1) and the E3 gene on viral growth (Expt. #2). The bars denote the region of modifications made to the E1 deletion.

5 Figure 6 shows an autoradiograph of viral DNA analysis following the viral mixing experiments described in Examples 6 and 7.

 Figures 7A, 7B and 7C are as follows: Figure 7A shows the hCMV-Flgag-bGHpA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Both E1 parallel and E1 antiparallel transgene orientation are represented. Figure 7B shows the hCMV-Flgag-SPA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Again, both E1 parallel and E1 antiparallel transgene orientation are represented. Figure 7C shows the mCMV-Flgag-bGHpA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Once again, both E1 parallel and E1 antiparallel transgene orientation are represented.

15 Figure 8A shows the experiment designed to test the effect of transgene orientation.

 Figure 8B shows the experiments designed to test the effect of polyadenylation signal.

20 Figure 9 shows viral DNA from the four adenoviral vectors tested (Example 12) at P5, following *Bst*E11 digestion.

 Figure 10 shows viral DNA analysis of passages 11 and 12 of MRKpAdHVE3, MRKAd5HIV-1gag, and MRKAd5HIV-1gagE3-.

 Figure 11 shows viral DNA analysis (*Hind*III digestion) of passage 6 MRKpAdHVE3 and MRKAd5HIV-1gag used to initiate the viral competition study. The last two lanes are passage 11 analysis of duplicate passages of the competition study (each virus at MOI of 280 viral particles).

 Figure 12 shows viral DNA analysis by *Hind* III digestion on high passage numbers for MRKAd5HIV-1gag in serum-containing media with collections made at specified times. The first lane shows the 1kb DNA size marker. The other lanes represent pre-plasmid control (digested with Pac1 and *Hind*III), MRKAd5HIV-1gag at P16, P19, and P21.

 Figure 13 shows serum anti-p24 levels at 3 wks post i.m. immunization of balb/c mice (n=10) with varying doses of several Adgag constructs: (A) MRK Ad5 HIV-1 gag (through passage 5); (B) MRKAd5 hCMV-FLgag-bGHpA (E3-); (C) MRKAd5 hCMV-FLgag-SPA (E3+); (D) MRKAd5 mCMV-FLgag-bGHpA (E3+);

(E) research lot (293 cell-derived) of Ad5HIV-1 gag; and (F) clinical lot (Ad5gagFN0001) of Ad5HIV-1 gag. Reported are the geometric mean titers (GMT) for each cohort along with the standard error bars.

Figure 14 shows a restriction map of the pMRKAd5HIV-1gag vector.

5 Figures 15A-X illustrates the nucleotide sequence of the pMRKAd5HIV-1gag vector (SEQ ID NO:27.[coding] and SEQ ID NO:28 [non-coding]).

Figures 16A-B shows a schematic representation of DNA vaccine expression vectors V1Jns (A) and V1Jns-tPA (B), which are utilized for HIV-1 gag, pol and nef constructs in various DNA/viral vector combined modality regimens as disclosed
10 herein.

Figures 17A-C shows the nucleotide (SEQ ID NO:3) and amino acid sequence (SEQ ID NO:4) of IA-Pol. Underlined codons and amino acids denote mutations, as listed in Table 1.

Figure 18 shows codon optimized nucleotide and amino acid sequences
15 through the fusion junction of tPA-pol inact(opt) (contained within SEQ ID NOs: 7 and 8, respectively). The underlined portion represents the NH₂-terminal region of IA-Pol.

Figures 19A-B show a nucleotide sequence comparison between wild type nef(jrfl) and codon optimized nef. The wild type nef gene from the jrfl isolate
20 consists of 648 nucleotides capable of encoding a 216 amino acid polypeptide. WT, wild type sequence (SEQ ID NO:19); opt, codon-optimized sequence (contained within SEQ ID NO:1). The Nef amino acid sequence is shown in one-letter code (SEQ ID NO:2).

Figures 20A-C show nucleotide sequences at junctions between nef coding
25 sequence and plasmid backbone of nef expression vectors V1Jns/nef (Figure 20A), V1Jns/nef(G2A,LLAA) (Figure 20B), V1Jns/tpanef (Figure 20C) and V1Jns/tpanef(LLAA) (Figure 20C, also). 5' and 3' flanking sequences of codon optimized nef or codon optimized nef mutant genes are indicated by bold/italic letters; nef and nef mutant coding sequences are indicated by plain letters. Also indicated (as
30 underlined) are the restriction endonuclease sites involved in construction of respective nef expression vectors. V1Jns/tpanef and V1Jns/tpanef(LLAA) have identical sequences at the junctions.

Figure 21 shows a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine 174
35 and 175 are the sites involved in myristylation and dileucine motif, respectively. For both versions of the tpanef fusion genes, the putative leader peptide cleavage sites are

indicated with "*", and a exogenous serine residue introduced during the construction of the mutants is underlined.

Figure 22 shows diagrammatically the construction of the pre-adenovirus plasmid construct, MRKAd5Pol.

5 Figure 23 shows diagrammatically the construction of the pre-adenovirus plasmid construct, MRKAd5Nef.

Figure 24 shows a comparison of clade B vs. clade C anti-gag T cell responses in clade B HIV-infected subjects.

10 Figure 25 shows a comparison of clade B vs. clade C anti-nef T cell responses in clade B HIV-infected subjects.

Figures 26A-AO illustrates the nucleotide sequence of the pMRKAd5HIV-1pol adenoviral vector (SEQ ID NO:32 [coding] and SEQ ID NO:33 [non-coding]), comprising the coding region of the inactivated pol gene (SEQ ID NO3).

15 Figures 27A-AM illustrates the nucleotide sequence of the pMRKAd5HIV-1 nef adenoviral vector (SEQ ID NO:34 [coding] and SEQ ID NO:35 [non-coding]), comprising the coding region of the inactivated pol gene (SEQ ID NO13).

Figure 28 shows the stability of MRKAd5 vectors comprising various promoter fragments (hCMV or mCMV) and terminations signals (bGH or SPA) in E3(+) or E3(-) backbones.

20 Figures 29A and B shows the anion-exchange HPLC viral particle concentrations of the freeze-thaw recovered cell associated virus at the 24, 36, 48, and 60 hpi time points (Figure 29A) and the timcourse QPA supernatant titers (Figure 29B) for MRKAd5gag, MRKAd5pol and MRKAd5nef.

25 Figure 30 shows the nucleotide sequence (SEQ ID NO:36) and amino acid sequence (SEQ ID NO:37) comprising the open reading frame of a representative tPA-gag fusion for use in the DNA and/or adenoviral vaccine disclosed herein.

30 Figure 31 shows the intracellular γ IFN staining of PBMCs collected at week 10 (post DNA prime) and week 30 (post Ad boost). The cells were stimulated overnight in the presence or absence of the gag peptide pool. They were subsequently stained using fluorescence-tagged anti-CD3, anti-CD8, anti-CD4, and anti- γ IFN monoclonal antibodies. Each plot shows all CD3+ T cells which were segregated in terms of positive staining for surface CD8 and γ IFN production. The numbers in the upper right and lower right quadrants of each plot are the percentages of CD3+ cells that were CD8+ γ IFN+ and CD4+ γ IFN+, respectively.

35 Figure 32 shows a comparison of single-modality adenovirus immunization with DNA + adjuvant prime/adenovirus boost immunization.

Figures 33A-B show the nucleotide sequence (SEQ ID NO: 38) of the open reading frame for the gag-IAPol fusion of Example 29.

Figures 34A-B show the protein sequence (SEQ ID NO:39) of the gag-IAPol fusion frame.

5

DETAILED DESCRIPTION OF THE INVENTION

A novel replication-defective, or "first generation," adenoviral vector suitable for use in gene therapy or nucleotide-based vaccine vectors is described. This vector is at least partially deleted in E1 and comprises a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between about base pair 342 (more preferably, 400) to about 458 (preferably, 1-450) and, preferably, 3511-3523 of a wild-type adenovirus sequence. It has been found that a vector of this description possesses enhanced growth characteristics, with approximately 5-10 fold greater amplification rates, and is more potent allowing lower doses of virus to be used to generate equivalent immunity. The vector, furthermore, generates a harvested recombinant adenovirus which shows greater cellular-mediated immune responses than replication-deficient vectors not comprising this region (basepairs 342-450). Adenoviral constructs derived from these vectors are, further, very stable genetically, particularly those comprising a transgene under the control of a hCMV promoter devoid of intron A. Viruses in accordance with this description were passaged continually and analyzed; see Example 12. Each virus analyzed maintained its correct genetic structure. Analysis was also carried out under propagation conditions similar to that performed in large scale production. Again, the vectors were found to possess enhanced genetic stability; see Figure 12. Following 21 passages, the viral DNA showed no evidence of rearrangement, and was highly reproducible from one production lot to the next. The outcome of all relevant tests indicate that the adenoviral vector is extremely well suited for large-scale production of recombinant, replication-deficient adenovirus, as shown herein with the data associated with Figure 28.

A preferred adenoviral vector in accordance with this description is a vector comprising basepairs 1-450, which is deleted in E3. This vector can accommodate up to approximately 7,500 base pairs of foreign DNA inserts (or exogenous genetic material). Another preferred vector is one retaining E3 which comprises basepairs 1-450. A preferred vector of this description is an E3+ vector comprising basepairs 1-450 and 3511-3523. This vector, when deleted of the region spanning basepairs 451-3510, can accommodate up to approximately, 4,850 base pairs of foreign DNA inserts

(or exogenous genetic material). The cloning capacities of the above vectors have been determined using 105% of the wildtype Ad5 sequence as the upper genome size limit.

Wildtype adenovirus serotype 5 is used as the basis for the specific basepair numbers provided throughout the specification. The wildtype adenovirus serotype 5 sequence is known and described in the art; *see*, Chroboczek *et al.*, 1992 *J. Virology* 186:280, which is hereby incorporated by reference. Accordingly, a particular embodiment of the instant invention is a vector based on the adenovirus serotype 5 sequence. One of skill in the art can readily identify the above regions in other adenovirus serotypes (e.g., serotypes 2, 4, 6, 12, 16, 17, 24, 31, 33, and 42), regions defined by basepairs corresponding to the above basepair positions given for adenovirus serotype 5. Accordingly, the instant invention encompasses all adenoviral vectors partially deleted in E1 comprising basepairs corresponding to 1-450 (particularly, 342-450) and, preferably, 3511-3523 of a wild-type adenovirus serotype 5 (Ad5) nucleic acid sequence. Particularly preferred embodiments of the instant invention are those derived from adenoviruses like Ad5 which are classified in subgroup C (e.g., Ad2).

Vectors in accordance with the instant invention are at least partially deleted in E1. Preferably the E1 region is completely deleted or inactivated. Most preferably, the region deleted of E1 is within basepairs 451-3510. It is to be noted that the extended 5' and 3' regions of the disclosed vectors are believed to effectively reduce the size of the E1 deletion of previous constructs without overlapping any part of the E1A/E1B gene present in the cell line used, i.e., the PER.C6[®] cell line transfected with base pairs 459-3510. Overlap of adenoviral sequences is avoided because of the possibility of recombination. One of ordinary skill in the art can certainly appreciate that the instant invention can, therefore, be modified if a different cell line transfected with a different segment of adenovirus DNA is utilized. For purposes of exemplification, a 5' region of base pairs 1 to up to 449 is more appropriate if a cell line is transfected with adenoviral sequence from base pairs 450-3510. This holds true as well in the consideration of segments 3' to the E1 deletion.

Preferred embodiments of the instant invention possess an intact E3 region (i.e., an E3 gene capable of encoding a functional E3). Alternate embodiments have a partially deleted E3, an inactivated E3 region, or a sequence completely deleted of E3. Applicants have found, in accordance with the instant invention, that virus comprising the E3 gene were able to amplify more rapidly compared with virus not comprising an E3 gene; see Figure 6 wherein a diagnostic CsCl band corresponding to the E3+ virus

tested (5,665 bp) was present in greater amount compared with the diagnostic band of 3,010 bp corresponding to the E3- virus. These results were obtained following a virus competition study involving mixing equal MOI ratio (1:1) of adenovectors both comprising the E3 gene and not comprising the E3 gene. This increased amplification capacity of the E3+ adenovectors was subsequently confirmed with growth studies; see Table 4A, wherein the E3+ virus exhibit amplification ratios of 470, 420 and 320 as compared with the 115 and 40-50 of the E3- constructs.

As stated above, vectors in accordance with the instant invention can accommodate up to approximately 4,850 base pairs of exogenous genetic material for an E3+ vector and approximately 7,500 base pairs for an E3- vector. Preferably, the insert brings the adenoviral vector as close as possible to a wild-type genomic size (e.g., for Ad5, 35,935 basepairs). It is well known that adenovirus amplifies best when they are close to their wild-type genomic size.

The genetic material can be inserted in an E1-parallel or an E1 anti-parallel orientation, as such is illustrated in Figure 7A, 7B, 7C and Figure 8A. Particularly preferred embodiments of the instant invention, have the insert in an E1-parallel orientation. Applicants have found, via competition experiments with plasmids containing transgenes in differing orientation (Figure 8A), that vector constructs with the foreign DNA insert in an E1-parallel orientation amplify better and actually out-compete E1-antiparallel-oriented transgenes. Viral DNA analysis of the mixtures at passage 3 and certainly at passage 6, showed a greater ratio of the virus carrying the transgene in the E1 parallel orientation as compared with the E1 anti-parallel version. By passage 10, the only viral species observed was the adenovector with the transgene in the E1 parallel orientation for both transgenes tested.

Adenoviral vectors in accordance with the instant invention are particularly well suited to effectuate expression of desired proteins, one example of which is an HIV protein, particularly an HIV full length gag protein. Exogenous genetic material encoding a protein of interest can exist in the form of an expression cassette. A gene expression cassette preferably comprises (a) a nucleic acid encoding a protein of interest; (b) a heterologous promoter operatively linked to the nucleic acid encoding the protein; and (c) a transcription terminator.

The transcriptional promoter is preferably recognized by an eukaryotic RNA polymerase. In a preferred embodiment, the promoter is a "strong" or "efficient" promoter. An example of a strong promoter is the immediate early human cytomegalovirus promoter (Chapman et al, 1991 *Nucl. Acids Res*19:3979-3986, which is incorporated by reference), preferably without intronic sequences. Most preferred

for use within the instant adenoviral vector is a human CMV promoter without intronic sequences, like intron A. Applicants have found that intron A, a portion of the human cytomegalovirus promoter (hCMV), constitutes a region of instability for adenoviral vectors. CMV without intron A has been found to effectuate (Examples 1-3) comparable expression capabilities *in vitro* when driving HIV gag expression and, furthermore, behaved equivalently to intron A-containing constructs in Balb/c mice *in vivo* with respect to their antibody and T-cell responses at both dosages of plasmid DNA tested (20 µg and 200 µg). Those skilled in the art will appreciate that any of a number of other known promoters, such as the strong immunoglobulin, or other eukaryotic gene promoters may also be used, including the EF1 alpha promoter, the murine CMV promoter, Rous sarcoma virus (RSV) promoter, SV40 early/late promoters and the beta-actin promoter.

In preferred embodiments, the promoter may also comprise a regulatable sequence such as the Tet operator sequence. This would be extremely useful, for example, in cases where the gene products are effecting a result other than that desired and repression is sought.

Preferred transcription termination sequences present within the gene expression cassette are the bovine growth hormone terminator/polyadenylation signal (bGHpA) and the short synthetic polyA signal (SPA) of 50 nucleotides in length, defined as follows: AATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGT-TTTTGTGTG (SEQ ID NO:26).

The combination of the CMV promoter (devoid of the intron A region) with the BGH terminator is particularly preferred although other promoter/terminator combinations in the context of FG adenovirus may also be used.

Other embodiments incorporate a leader or signal peptide into the transgene. A preferred leader is that from the tissue-specific plasminogen activator protein, tPA. Examples include but are not limited to the various tPA-gag, tPA-pol and tPA-nef adenovirus-based vaccines disclosed throughout this specification.

In view of the improved adenovirus vectors described herein, an essential portion of the present invention are adenoviral-based HIV vaccines comprising said adenovirus backbones which may be administered to a mammalian host, preferably a human host, in either a prophylactic or therapeutic setting. The HIV vaccines of the present invention, whether administered alone or in combination regimens with other viral- or non-viral-based DNA vaccines, should elicit potent and broad cellular immune responses against HIV that will either lessen the likelihood of persistent virus infection and/or lead to the establishment of a clinically significant lowered virus load

subject to HIV infection or in combination with HAART therapy, mitigate the effects of previously established HIV infection (antiviral immunotherapy(ARI)). While any HIV antigen (e.g., gag, pol, nef, gp160, gp41, gp120, tat, rev, etc.) may be utilized in the herein described recombinant adenoviral vectors, preferred embodiments include the codon optimized p55 gag antigen (herein exemplified as MRKAd5gag), pol and nef. Sequences based on different Clades of HIV-1 are suitable for use in the instant invention, most preferred of which are Clade B and Clade C. Particularly preferred embodiments are those sequences (especially, codon-optimized sequences) based on consensus Clade B sequences. Preferred versions of the MRKAd5pol and MRKAd5nef series of adenoviral vaccines will encode modified versions of pol or nef, as discussed herein. Preferred embodiments of the MRKAd5HIV-1 vectors carrying HIV envelope genes and modifications thereof comprise the HIV codon-optimized *env* sequences of PCT International Applications PCT/US97/02294 and PCT/US97/10517, published August 28, 1997 (WO 97/31115) and December 24, 1997, respectively; both documents of which are hereby incorporated by reference.

A most preferred aspect of the instant invention is the disclosed use of the adenoviral vector described above to effectuate expression of HIV gag. Sequences for many genes of many HIV strains are publicly available in GENBANK and primary, field isolates of HIV are available from the National Institute of Allergy and Infectious Diseases (NIAID) which has contracted with Quality Biological (Gaithersburg, MD) to make these strains available. Strains are also available from the World Health Organization (WHO), Geneva Switzerland. It is preferred that the gag gene be from an HIV-1 strain (CAM-1; Myers et al, eds. "Human Retroviruses and AIDS: 1995, IIA3-IIA19, which is hereby incorporated by reference). This gene closely resembles the consensus amino acid sequence for the clade B (North American/European) sequence. Therefore, it is within the purview of the skilled artisan to choose an appropriate nucleotide sequence which encodes a specific HIV gag antigen, or immunologically relevant portion thereof. As shown in Example 25, a clade B or clade C based p55 gag antigen will potentially be useful on a global scale. As noted herein, the transgene of choice for insertion in to a DNA or MRKAd-based adenoviral vector of the present invention is a codon optimized version of p55 gag. Such a MRKAd5gag adenoviral vector is documented in Example 11 and is at least referred to herein as MRKAd5HIV-1gag. Of course, additional versions are contemplated, including but not limited to modifications such as promoter (e.g., mCMV for hCMV) and/or pA-terminations signal (SPA for bGH) switching, as well as generating MRK Ad5 backbones with or without deletion of the Ad5 E3 gene.

The present invention also relates a series of MRKAd5pol-based adenoviral vaccines which are shown herein to generate cellular immune responses subsequent to administration in mice and non-human primate studies. Several of the MRKAd5pol series are exemplified herein. One such adenoviral vector is referred to as

5 MRKAd5hCMV-inact opt pol(E3+), which comprises the MRKAd5 backbone, the hCMV promoter (no intron A), an inactivated pol transgene, and contains the Ad5 E3 gene in the adenoviral backbone. A second exemplified pre-adenovirus plasmid and concomitant virus is referred to as MRKAd5hCMV-inact opt pol(E3-), which is identical to the former adenoviral vector except that the E3 is deleted. Both

10 constructions contain a codon optimized, inactivated version of HIV-1 Pol, wherein at least the entire coding region is disclosed herein as SEQ ID NO:3 and the expressed protein is shown as SEQ ID NO:4 (see also Figure 17A-C and Table 1, which show targeted deletion for inactivated pol. This and other preferred codon optimized versions of HIV Pol as disclosed herein are essentially as described in U.S.

15 Application Serial No. 09/745,221, filed December 21, 2000 and PCT International Application PCT/US00/34724, also filed December 21, 2000, both documents which are hereby incorporated by reference. As disclosed in the above-mentioned documents, the open reading frame for these codon-optimized HIV-1 Pol-based DNA vaccines are represented by codon optimized DNA molecules encoding codon

20 optimized HIV-1 Pol (e.g. SEQ ID NO:2), codon optimized HIV-1 Pol fused to an amino terminal localized leader sequence (e.g. SEQ ID NO:6), and especially preferable, and exemplified by the MRKAd5-Pol construct in e.g., Example 19, biologically inactivated pol ("inact opt Pol"; e.g., SEQ ID NO:4) which is devoid of significant PR, RT, RNase or IN activity associated with wild type Pol. In addition, a

25 construct related to SEQ ID NO:4 is contemplated which contains a leader peptide at the amino terminal region of the IA Pol protein. A specific construct is ligated within an appropriate DNA plasmid vector containing regulatory regions operatively linked to the respective HIV-1 Pol coding region, with or without a nucleotide sequence encoding a functional leader peptide. To this end, various HIV-1 Pol constructs

30 disclosed herein relate to open reading frames for cloning to the enhanced first generation Ad vectors of the present invention (such a series of MRKAd5pol adenoviral vaccine vectors), including but not limited to wild type Pol (comprising the DNA molecule encoding WT opt Pol, as set forth in SEQ ID NO:2), tPA-opt WTPol, (comprising the DNA molecule encoding tPA Pol, as set forth in SEQ ID NO:6), inact

35 opt Pol (comprising the DNA molecule encoding IA Pol, as set forth in SEQ ID NO:4), and tPA-inact opt Pol, (comprising the DNA molecule encoding tPA-inact opt

Pol, as set forth in SEQ ID NO:8). The pol-based versions of enhanced first generation adenovirus vaccines elicit CTL and Th cellular immune responses upon administration to the host, including primates and especially humans. As noted in the above, an effect of the cellular immune-directed vaccines of the present invention should be a lower transmission rate to previously uninfected individuals and/or reduction in the levels of the viral loads within an infected individual, so as to prolong the asymptomatic phase of HIV-1 infection.

The present invention further relates to a series of MRKAd5nef-based adenoviral vaccines which, similar to HIV gag and pol antigens, generate cellular immune responses subsequent to administration in mice and non-human primate studies. The MRKAd5nef series are exemplified herein by utilizing the improved MRK adenoviral backbone in combination with modified versions of HIV nef. These exemplified MRKAd5nef vectors are as follows: (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+), which comprises the improved MRKAd5 backbone, a human CMV promoter an intact Ad5 E3 gene and a modified nef gene: (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+), which is the same as (1) above but substituting a murine CMV promoter for a human CMV promoter; and (3) MRKAd5mCMV-tpanef(LLAA) (E3+), which is the same as (2) except that the nef transgene is tpanef(LLAA). Codon optimized versions of HIV-1 Nef and HIV-1 Nef modifications are essentially as described in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed December 15, 2000, both documents which are hereby incorporated by reference. Particular embodiments of codon optimized Nef and Nef modifications relate to a DNA molecule encoding HIV-1 Nef from the HIV-1 jf1 isolate wherein the codons are optimized for expression in a mammalian system such as a human. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:9, while the expressed open reading frame is disclosed herein as SEQ ID NO:10. Another embodiment of Nef-based coding regions for use in the adenoviral vectors of the present invention comprise a codon optimized DNA molecule encoding a protein containing the human plasminogen activator (tpa) leader peptide fused with the NH₂-terminus of the HIV-1 Nef polypeptide. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:11, while the expressed open reading frame is disclosed herein as SEQ ID NO:12. Another modified Nef optimized coding region relates to a DNA molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175, herein

described as opt nef (G2A, LLAA). The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:13, while the expressed open reading frame is disclosed herein as SEQ ID NO:14. MRKAd5nef vectors (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+) and (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+) contain this
5 transgene. An additional embodiment relates to a DNA molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation site and dileucine motif have been deleted, as well as comprising a tPA leader peptide. This DNA molecule, opt tpanef (LLAA), comprises an open reading frame which encodes a Nef protein containing a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef
10 (jfrl), wherein Leu-174 and Leu-175 are substituted with Ala-174 and Ala-175, herein referred to as opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, while the expressed open reading frame is disclosed herein as SEQ ID NO:16. The MRKAd5nef vector "MRKAd5mCMV-tpanef(LLAA) (E3+)" contains this transgene.

Along with the improved MRKAd5gag adenovirus vaccine vector described
15 herein, generation of a MRKAd5pol and MRKAd5nef adenovirus vector provide for enhanced HIV vaccine capabilities. Namely, the generation of this trio of adenoviral vaccine vectors, all shown to generate effective cellular immune responses subsequent to host administration, provide for the ability to administer these vaccine candidates not only alone, but preferably as part of a divalent (i.e., gag and nef, gag and pol, or
20 pol and nef components) or a trivalent vaccine (i.e., gag, pol and nef components). Therefore, a preferred aspect of the present invention are vaccine formulations and associated methods of administration and concomitant generation of host cellular immune responses associated with formulating three separate series of MRKAd5-based adenoviral vector vaccines. Of course, this MRKAd5 vaccine series based on
25 distinct HIV antigens promotes expanded opportunities for formulation of a divalent or trivalent vaccine, or possibly administration of separate formulations of one or more monovalent or divalent formulations within a reasonable window of time. It is also within the scope of the present invention to embark on combined modality regimes which include multiple but distinct components from a specific antigen. An
30 example, but certainly not a limitation, would be separate MRKAd5pol vectors, with one vaccine vector expressing wild type Pol (SEQ ID NO:2) and another MRKAd5pol vector expressing inactivated Pol (SEQ ID NO:6). Another example might be separate MRKAd5nef vectors, with one vaccine vector expressing the tPA/LLAA version of Nef (SEQ ID NO:16) and another MRKAd5nef vector
35 expressing the G2A,LLAA modified version of Nef (SEQ ID NO:14). Therefore, the MRKAd5 adenoviral vectors of the present invention may be used in combination

with multiple, distinct HIV antigen classes. Each HIV antigen class is subject to sequence manipulation, thus providing for a multitude of potential vaccine combinations; and such combinations are within the scope of the present invention. The utilization of such combined modalities vaccine formulation and administration
5 increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a single modality regimen.

The present invention also relates to application of a mono-, dual-, or tri-modality administration regime of the MRKAd5gag, pol and nef adenoviral vaccine series in a prime/boost vaccination schedule. This prime/boost schedule may include
10 any reasonable combination of the MRKAd5gag, pol and nef adenoviral vaccine series disclosed herein. In addition, a prime/boost regime may also involve other viral and/or non-viral DNA vaccines. A preferable addition to an adenoviral vaccine vector regime includes but is not limited to plasmid DNA vaccines, especially DNA plasmid vaccines that contain at least one of the codon optimized gag, pol and nef
15 constructions, as disclosed herein.

Therefore, one aspect of this invention is the administration of the adenoviral vector containing the optimized gag gene in a prime/boost regiment in conjunction with a plasmid DNA encoding gag. To distinguish this plasmid from the adenoviral-containing shuttle plasmids used in the construction of an adenovirus vector, this
20 plasmid will be referred to as a "vaccine plasmid" or "DNA plasmid vaccine". Preferred vaccine plasmids for use in this administration protocol are disclosed in pending U.S. patent application 09/017,981, filed February 3, 1998 and WO98/34640, published August 13, 1998, both of which are hereby incorporated by reference. Briefly, the preferred vaccine plasmid is designated V1Jns-FLgag, which expresses
25 the same codon-optimized gag gene as the adenoviral vectors of this invention (see Figure 2 for the nucleotide sequence of the exemplified optimized codon version of full length p55 gag). The vaccine plasmid backbone, designated V1Jns contains the CMV immediate-early (IE) promoter and intron A, a bovine growth hormone-derived polyadenylation and transcription termination sequence as the gene expression
30 regulatory elements, and a minimal pUC backbone; see Montgomery *et al.*, 1993, *DNA Cell Biol.* 12:777-783. The pUC sequence permits high levels of plasmid production in *E. coli* and has a neomycin resistance gene in place of an ampicillin resistance gene to provide selected growth in the presence of kanamycin. Alternatively, a vaccine plasmid which has the CMV promoter deleted of intron A can
35 be used. Those of skill in the art will recognize that alternative vaccine plasmid

vectors may be easily substituted for these specific constructs, and this invention specifically envisions use of such alternative plasmid DNA vaccine vectors.

Another aspect of the present invention is a prime/boost regimen which includes a vaccine plasmid which encodes an HIV pol antigen, preferably a codon optimized form of pol and also preferably a vaccine plasmid which comprises a
5 nucleotide sequence which encodes a Pol antigen selected from the group of Pol antigens as shown in SEQ ID NOs: 2, 4, 6 and 8. The variety of potential DNA plasmid vaccines which encode various biologically active forms of HIV-1 Pol, wherein administration, intracellular delivery and expression of the HIV-1 Pol gene of
10 interest elicits a host CTL and Th response. The preferred synthetic DNA molecules of the present invention encode codon optimized wild type Pol (without Pro activity) and various codon optimized inactivated HIV-1 Pol proteins. The HIV-1 *pol* open reading disclosed herein are especially preferred for pharmaceutical uses, especially for human administration as delivered via a recombinant adenoviral vaccine,
15 especially an enhanced first generation recombinant adenoviral vaccine as described herein. Several embodiments of this portion of the invention are provided in detail below, namely DNA molecules which comprise a HIV-1 pol open reading frame, whether encoding full length pol or a modification or fusion as described herein, wherein the codon usage has been optimized for expression in a mammal, especially a
20 human. Again, these DNA sequences are positioned appropriately within a recombinant adenoviral vector, such as the exemplified recombinant adenoviral vector described herein, so as to promote expression of the respective HIV-1 Pol gene of interest, and subsequent to administration, elicit a host CTL and Th response. Again, these preferred, but in no way limiting, pol genes are as disclosed herein and
25 essentially as described in U.S. Application Serial No. 09/745,221, filed December 21, 2000 and PCT International Application PCT/US00/34724, also filed December 21, 2000, both documents which are hereby incorporated by reference.

A third series of vaccine plasmids which are useful in a combined modality and/or prime/boost regimen are vaccine plasmids which encode an HIV nef antigen or
30 biologically and/or immunologically relevant modification thereof. As noted elsewhere, preferred vaccine plasmids contain a codon optimized form of nef and also preferably comprise a nucleotide sequence which encodes a Nef antigen selected from the group of Nef antigens as shown in SEQ ID NOs: 10, 12, 14 and 16. These preferred nef coding regions are disclosed herein, as well as being described in U.S.
35 Application Serial No. 09/738,782, filed December 15, 2000 and PCT International

Application PCT/US00/34162, also filed December 15, 2000, both documents which are hereby incorporated by reference.

Therefore, the adenoviral vaccines and plasmid DNA vaccines of this invention may be administered alone, or may be part of a prime and boost administration regimen. A mixed modality priming and booster inoculation scheme will result in an enhanced immune response, particularly if pre-existing anti-vector immune responses are present. This one aspect of this invention is a method of priming a subject with the plasmid vaccine by administering the plasmid vaccine at least one time, allowing a predetermined length of time to pass, and then boosting by administering the adenoviral vaccine. Multiple primings typically, 1-4, are usually employed, although more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. In experiments with rhesus monkeys, the animals were primed four times with plasmid vaccines, then were boosted 4 months later with the adenoviral vaccine. Their cellular immune response was notably higher than that of animals which had only received adenoviral vaccine. The use of a priming regimen may be particularly preferred in situations where a person has a pre-existing anti-adenovirus immune response.

Furthermore and in the alternative, multiple HIV-1 viral antigens, such as the MRKAd5 adenoviral vaccines disclosed herein, may be ligated into a proper shuttle plasmid for generation of a pre-adenoviral plasmid comprising multiple open reading frames. For example a trivalent vector may comprise a gag-pol-nef fusion, in either a E3(-) or E3(+) background, preferably a E3 deleted backbone, or possibly a "2+1" divalent vaccine, such as a gag-pol fusion (i.e., codon optimized p55 gag and inactivated optimized pol; Example 29 and Table 25) within the same MRKAd5 backbone, with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the two open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES), as disclosed in International Publication No. WO 95/24485, which is hereby incorporated by reference. Figure 9 shows that the use of multiple promoters and termination sequences provide for similar growth properties, while Figure 28 shows that these MRKAd5gag-based vectors are also stable at least through passage 21. In the absence of the use of IRES-based technology, it is preferred that a distinct promoter be used to support each respective open reading frame, so as to best preserve vector stability. As examples, and certainly not as limitations, potential multiple transgene vaccines may

include a three transgene vector such as hCMV-gagpol-bGHpA + mCMV-nef-SPA in an E3 deleted backbone or hCMV-gagpol-bGHpA + mCMV-nef-SPA(E3+).

Potential "2+1" divalent vaccines of the present invention might be a hCMV-gag-bGHpA + mCMV-nef-SPA in an E3+ backbone (vector #1) in combination with

5 hCMV-pol-bGHpA in an E3+ backbone (vector #2), with all transgenes in the E1 parallel orientation. Fusion constructs other than the gag-pol fusion described above are also suitable for use in various divalent vaccine strategies and can be composed of any two HIV antigens fused to one another (*e.g.*, nef-pol and gag-nef). These adenoviral compositions are, as above, preferably delivered along with an adenoviral
10 composition comprising an additional HIV antigen in order to diversify the immune response generated upon administration. Therefore, a multivalent vaccine delivered in a single, or possible second, adenoviral vector is certainly contemplated as part of the present invention. Again, this mode of administration is another example of whereby an efficacious adenovirus-based HIV-1 vaccine may be administered via a
15 combined modality regime. It is important to note, however, that in terms of deciding on an insert for the disclosed adenoviral vectors, due consideration must be dedicated to the effective packaging limitations of the adenovirus vehicle. Adenovirus has been shown to exhibit an upper cloning capacity limit of approximately 105% of the wildtype Ad5 sequence.

20 Regardless of the gene chosen for expression, it is preferred that the sequence be "optimized" for expression in a human cellular environment. A "triplet" codon of four possible nucleotide bases can exist in 64 variant forms. That these forms provide the message for only 20 different amino acids (as well as transcription initiation and termination) means that some amino acids can be coded for by more than one codon.
25 Indeed, some amino acids have as many as six "redundant", alternative codons while some others have a single, required codon. For reasons not completely understood, alternative codons are not at all uniformly present in the endogenous DNA of differing types of cells and there appears to exist variable natural hierarchy or "preference" for certain codons in certain types of cells. As one example, the amino
30 acid leucine is specified by any of six DNA codons including CTA, CTC, CTG, CTT, TTA, and TTG (which correspond, respectively, to the mRNA codons, CUA, CUC, CUG, CUU, UUA and UUG). Exhaustive analysis of genome codon frequencies for microorganisms has revealed endogenous DNA of *E. coli* most commonly contains the CTG leucine-specifying codon, while the DNA of yeasts and slime molds most
35 commonly includes a TTA leucine-specifying codon. In view of this hierarchy, it is generally held that the likelihood of obtaining high levels of expression of a leucine-

rich polypeptide by an *E. coli* host will depend to some extent on the frequency of codon use. For example, a gene rich in TTA codons will in all probability be poorly expressed in *E. coli*, whereas a CTG rich gene will probably highly express the polypeptide. Similarly, when yeast cells are the projected transformation host cells
5 for expression of a leucine-rich polypeptide, a preferred codon for use in an inserted DNA would be TTA.

The implications of codon preference phenomena on recombinant DNA techniques are manifest, and the phenomenon may serve to explain many prior failures to achieve high expression levels of exogenous genes in successfully
10 transformed host organisms—a less "preferred" codon may be repeatedly present in the inserted gene and the host cell machinery for expression may not operate as efficiently. This phenomenon suggests that synthetic genes which have been designed to include a projected host cell's preferred codons provide a preferred form of foreign genetic material for practice of recombinant DNA techniques. Thus, one aspect of
15 this invention is an adenovirus vector or adenovirus vector in some combination with a vaccine plasmid where both specifically include a gene which is codon optimized for expression in a human cellular environment. As noted herein, a preferred gene for use in the instant invention is a codon-optimized HIV gene and, particularly, HIV gag, pol or nef.

20 Adenoviral vectors in accordance with the instant invention can be constructed using known techniques, such as those reviewed in Hitt et al, 1997 "Human Adenovirus Vectors for Gene Transfer into Mammalian Cells" *Advances in Pharmacology* 40:137-206, which is hereby incorporated by reference.

In constructing the adenoviral vectors of this invention, it is often convenient
25 to insert them into a plasmid or shuttle vector. These techniques are known and described in Hitt et al., *supra*. This invention specifically includes both the adenovirus and the adenovirus when inserted into a shuttle plasmid.

Preferred shuttle vectors contain an adenoviral portion and a plasmid portion. The adenoviral portion is essentially the same as the adenovirus vector discussed
30 *supra*, containing adenoviral sequences (with non-functional or deleted E1 and E3 regions) and the gene expression cassette, flanked by convenient restriction sites. The plasmid portion of the shuttle vector often contains an antibiotic resistance marker under transcriptional control of a prokaryotic promoter so that expression of the antibiotic does not occur in eukaryotic cells. Ampicillin resistance genes, neomycin
35 resistance genes and other pharmaceutically acceptable antibiotic resistance markers may be used. To aid in the high level production of the polynucleotide by

fermentation in prokaryotic organisms, it is advantageous for the shuttle vector to contain a prokaryotic origin of replication and be of high copy number. A number of commercially available prokaryotic cloning vectors provide these benefits. It is desirable to remove non-essential DNA sequences. It is also desirable that the vectors
5 not be able to replicate in eukaryotic cells. This minimizes the risk of integration of polynucleotide vaccine sequences into the recipients' genome. Tissue-specific promoters or enhancers may be used whenever it is desirable to limit expression of the polynucleotide to a particular tissue type.

In one embodiment of this invention, the pre-plasmids (e.g., pMRKAd5pol,
10 pMRKAd5nef and pMRKAd5gag were generated by homologous recombination using the MRKHVE3 (and MRKHVO for the E3- version) backbones and the appropriate shuttle vector, as shown for pMRKAd5pol in Figure 22 and for pMRKAd5nef in Figure 23. The plasmid in linear form is capable of replication after entering the PER.C6[®] cells and virus is produced. The infected cells and media were
15 harvested after viral replication was complete.

Viral vectors can be propagated in various E1 complementing cell lines, including the known cell lines 293 and PER.C6[®]. Both these cell lines express the adenoviral E1 gene product. PER.C6[®] is described in WO 97/00326 (published January 3, 1997) and issued U.S. Patent No. 6,033,908, both of which are hereby
20 incorporated by reference. It is a primary human retinoblast cell line transduced with an E1 gene segment that complements the production of replication deficient (FG) adenovirus, but is designed to prevent generation of replication competent adenovirus by homologous recombination. Cells of particular interest have been stably transformed with a transgene that encodes the AD5E1A and E1B gene, like PER.C6[®],
25 from 459 bp to 3510 bp inclusive. 293 cells are described in Graham et al., 1977 *J. Gen. Virol* 36:59-72, which is hereby incorporated by reference. As stated above, consideration must be given to the adenoviral sequences present in the complementing cell line used. It is important that the sequences not overlap with that present in the vector if the possibility of recombination is to be minimized.

It has been found that vectors generated in accordance with the above
30 description are more effective in inducing an immune response and, thus, constitute very promising vaccine candidates. More particularly, it has been found that first generation adenoviral vectors in accordance with the above description carrying a codon-optimized HIV gag gene, regulated with a strong heterologous promoter can be
35 used as human anti-HIV vaccines, and are capable of inducing immune responses.

Standard techniques of molecular biology for preparing and purifying DNA constructs enable the preparation of the DNA immunogens of this invention.

A vaccine composition comprising an adenoviral vector in accordance with the instant invention may contain physiologically acceptable components, such as
5 buffer, normal saline or phosphate buffered saline, sucrose, other salts and polysorbate. One preferred formulation has: 2.5-10 mM TRIS buffer, preferably about 5 mM TRIS buffer; 25-100 mM NaCl, preferably about 75 mM NaCl; 2.5-10% sucrose, preferably about 5% sucrose; 0.01 -2 mM $MgCl_2$; and 0.001%-0.01% polysorbate 80 (plant derived). The pH should range from about 7.0-9.0, preferably
10 about 8.0. One skilled in the art will appreciate that other conventional vaccine excipients may also be used to make the formulation. The preferred formulation contains 5mM TRIS, 75 mM NaCl, 5% sucrose, 1mM $MgCl_2$, 0.005% polysorbate 80 at pH 8.0. This has a pH and divalent cation composition which is near the optimum for Ad5 stability and minimizes the potential for adsorption of virus to a glass surface.
15 It does not cause tissue irritation upon intramuscular injection. It is preferably frozen until use.

The amount of adenoviral particles in the vaccine composition to be introduced into a vaccine recipient will depend on the strength of the transcriptional and translational promoters used and on the immunogenicity of the expressed gene
20 product. In general, an immunologically or prophylactically effective dose of 1×10^7 to 1×10^{12} particles and preferably about 1×10^{10} to 1×10^{11} particles is administered directly into muscle tissue. Subcutaneous injection, intradermal introduction, impression through the skin, and other modes of administration such as intraperitoneal, intravenous, or inhalation delivery are also contemplated. It is also
25 contemplated that booster vaccinations are to be provided. Following vaccination with HIV adenoviral vector, boosting with a subsequent HIV adenoviral vector and/or plasmid may be desirable. Parenteral administration, such as intravenous, intramuscular, subcutaneous or other means of administration of interleukin-12 protein, concurrently with or subsequent to parenteral introduction of the vaccine
30 compositions of this invention is also advantageous.

The adenoviral vector and/or vaccine plasmids of this invention polynucleotide may be unassociated with any proteins, adjuvants or other agents which impact on the recipients' immune system. In this case, it is desirable for the vector to be in a physiologically acceptable solution, such as, but not limited to, sterile
35 saline or sterile buffered saline. Alternatively, the vector may be associated with an adjuvant known in the art to boost immune responses (i.e., a "biologically effective"

adjuvant), such as a protein or other carrier. Vaccine plasmids of this invention may, for instance, be delivered in saline (e.g., PBS) with or without an adjuvant. Preferred adjuvants are Alum or CRL1005 Block Copolymer. Agents which assist in the cellular uptake of DNA, such as, but not limited to, calcium ions, may also be used to advantage. These agents are generally referred to herein as transfection facilitating reagents and pharmaceutically acceptable carriers. Techniques for coating microprojectiles coated with polynucleotide are known in the art and are also useful in connection with this invention.

This invention also includes a prime and boost regimen wherein a first adenoviral vector is administered, then a booster dose is given. The booster dose may be repeated at selected time intervals. Alternatively, a preferred inoculation scheme comprises priming with a first adenovirus serotype and then boosting with a second adenovirus serotype. More preferably, the inoculation scheme comprises priming with a first adenovirus serotype and then boosting with a second adenovirus serotype, wherein the first and second adenovirus serotypes are classified within separate subgroups of adenoviruses. The above prime/boost schemes are particularly preferred in those situations where a preexisting immunity is identified to the adenoviral vector of choice. In this type of scheme, the individual or population of individuals is primed with an adenovirus of a serotype other than that to which the preexisting immunity is identified. This enables the first adenovirus to effectuate sufficient expression of the transgene while evading existing immunity to the second adenovirus (the boosting adenovirus) and, further, allows for the subsequent delivery of the transgene via the boosting adenovirus to be more effective. Adenovirus serotype 5 is one example of a virus to which such a scheme might be desirable. In accordance with this invention, therefore, one might decide to prime with a non-group C adenovirus (e.g., Ad12, a group A adenovirus, Ad24, a group D adenovirus, or Ad35, a group B adenovirus) to evade anti-Ad5 immunity and then boost with Ad5, a group C adenovirus. Another preferred embodiment involves administration of a different adenovirus (including non-human adenovirus) vaccine followed by administration of the adenoviral vaccines disclosed. In the alternative, a viral antigen of interest can be first delivered via a viral vaccine other than an adenovirus-based vaccine, and then followed with the adenoviral vaccine disclosed. Alternative viral vaccines include but are not limited to pox virus and venezuelan equine encephalitis virus.

A large body of human and animal data supports the importance of cellular immune responses, especially CTL in controlling (or eliminating) HIV infection. In humans, very high levels of CTL develop following primary infection and correlate

with the control of viremia. Several small groups of individuals have been described who are repeatedly exposed to HIV by remain uninfected; CTL has been noted in several of these cohorts. In the SIV model of HIV infection, CTL similarly develops following primary infection, and it has been demonstrated that addition of anti-CD8 monoclonal antibody abrogated this control of infection and leads to disease progression. This invention uses adenoviral vaccines alone or in combination with plasmid vaccines to induce CTL.

The following non-limiting Examples are presented to better illustrate the invention.

EXAMPLE 1

Removal of the Intron A Portion of the hCMV Promoter

GMP grade pVJnsHIVgag was used as the starting material to amplify the hCMV promoter. PVIJnsHIVgag is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone; see Montgomery *et al.*, *supra* for a description of the plasmid backbone. The amplification was performed with primers suitably positioned to flank the hCMV promoter. A 5' primer was placed upstream of the *MscI* site of the hCMV promoter and a 3' primer (designed to contain the *BglII* recognition sequence) was placed 3' of the hCMV promoter. The resulting PCR product (using high fidelity *Taq* polymerase) which encompassed the entire hCMV promoter (minus intron A) was cloned into TOPO PCR blunt vector and then removed by double digestion with *MscI* and *BglII*. This fragment was then cloned back into the original GMP grade pV1JnsHIVgag plasmid from which the original promoter, intron A, and the gag gene were removed following *MscI* and *BglII* digestion. This ligation reaction resulted in the construction of a hCMV promoter (minus intron A) + bGHpA expression cassette within the original pV1JnsHIVgag vector backbone. This vector is designated pVJnsCMV(no intron).

The FLgag gene was excised from pV1JnsHIVgag using *BglII* digestion and the 1,526 bp gene was gel purified and cloned into pV1JnsCMV(no intron) at the *BglII* site. Colonies were screened using *SmaI* restriction enzymes to identify clones that carried the FLgag gene in the correct orientation. This plasmid, designated pV1JnsCMV(no intron)-FLgag-bGHpA, was fully sequenced to confirm sequence integrity.

Two additional transgenes were also constructed. The plasmid, pV1JnsCMV(no intron)-FLgag-SPA, is identical to pV1JnsCMV(no intron)-FLgag-bGHpA except that the bovine growth hormone polyadenylation signal has been replaced with a short synthetic polyA signal (SPA) of 50 nucleotides in length. The sequence of the SPA is as shown, with the essential components (poly(A) site, (GT)_n, and (T)_n; respectively) underlined:

AATAAAAGATCTTTATTTTCATTAGATCTGTGTG TTGGTTTTTTGTGTG
(SEQ ID NO:18).

The plasmid, pV1Jns-mCMV-FLgag-bGHpA, is identical to the pV1JnsCMV(no intron)-FLgag-bGHpA except that the hCMV promoter has been removed and replaced with the murine CMV (mCMV) promoter.

Figure 3 diagrammatically shows the new transgene constructs in comparison with the original transgene.

EXAMPLE 2

Gag Expression Assay for Modified Gag Transgenes

Gag Elisa was performed on culture supernatants obtained from transient tissue culture transfection experiments in which the two new hCMV-containing plasmid constructs, pV1JnsCMV(no intron)-FLgag-bGHpA and pV1JnsCMV(no intron)-FLgag-SPA, both devoid of intron A, were compared to pV1JnsHIVgag which, as noted above possesses the intron A as part of the hCMV promoter. Table 2 below shows the *in vitro* gag expression data of the new gag plasmids compared with the GMP grade original plasmid. The results displayed in Table 2 show that both of the new hCMV gag plasmid constructs have expression capacities comparable to the original plasmid construct which contains the intron A portion of the hCMV promoter.

Table 2: *In vitro* DNA transfection of original and new plasmid HIV-1 gag constructs.

Plasmid	$\mu\text{g gag}/10^6 \text{ COS cells}/5\mu\text{g DNA}/48 \text{ hr}$
HIVFL-gagPR9901 ^a	10.8
pV1Jns-hCMV-FLgag-bGHpA ^b	16.6
pV1Jns-hCMV-FLgag-SPA ^{b,c}	12.0

^a GMP grade pV1Jns-hCMVintronA-FLgag-bGHpA.

5 ^b New plasmid constructions that have the intron A portion removed from the hCMV promoter.

^c In this construct the bGH terminator has been replaced with the short synthetic polyadenylation signal (SPA)

10 EXAMPLE 3

Rodent (Balb/c) Study for Modified gag Transgenes

A rodent study was performed on the two new plasmid constructs described above – pV1JnsCMV(no intron)-FLgag-bGHpA and pV1JnsCMV(no intron)-FLgag-SPA - in order to compare them with the construct described above
 15 possessing the intron A portion of the CMV promoter, pV1JnsHIVgag. Gag antibody and ELISPOT responses (described in PCT International Application No. PCT/US00/18332 (WO 01/02607) filed July 3, 2000, claiming priority to U.S. Provisional Application Serial No. 60/142,631, filed July 6, 1999 and U.S. Application Serial No. 60/148,981, filed August 13, 1999, all three applications which
 20 are hereby incorporated by reference) were measured. The results displayed in Table 3 below, show that the new plasmid constructs behaved equivalently to the original construct in Balb/c mice with respect to their antibody and T-cell responses at both dosages of plasmid DNA tested, 20 μg and 200 μg .

EXAMPLE 4

Table 3: HIV191: Immunogenicity of V1Jns-gag under different promoter and termination control elements.

DNA ^a Promoter/terminator	Dose, ug ^b	Anti-p24 Titers (3 Wk PD1) ^c			SFC/10 ⁶ Cells (4 Wk PD1) ^d		
		GMT	+SE	-SE	Media	gag197-205	p24
HIVFL-gagPR9901 (GMP grade)	200	12800	4652	3412	2(2)	129(19)	30(11)
	20	5572	1574	1227	0	56(9)	25(6)
pV1Jns-hCMV- FL-gag-bGHpA	200	11143	2831	2257	0	98(5)	12(6)
	20	7352	2808	2032	0	73(9)	11(6)
pV1Jns-hCMV- FL-gag-SPA	200	16890	5815	4326	1(1)	94(4)	26(7)
	20	5971	5361	2825	0	85(17)	38(10)
Naïve	0	123	50	36	0	0	0

^aIn PBS^bi.m. Injections into both quads, 50 µL per quad^cn=10; GMT, geometric mean titer; SE, standard. error^dn=5, pooled spleens; mean of triplicate wells and standard. deviation. in parentheses;

Construction of the Modified Shuttle Vector -"MRKpdeIE1 Shuttle"

The modifications to the original Ad5 shuttle vector (pdeIE1sp1A; a vector comprising Ad5 sequences from basepairs 1-341 and 3524-5798, with a multiple cloning region between nucleotides 341 and 3524 of Ad5, included the following three manipulations carried out in sequential cloning steps as follows:

- (1) The left ITR region was extended to include the *Pac*1 site at the junction between the vector backbone and the adenovirus left ITR sequences. This allow for easier manipulations using the bacterial homologous recombination system.
- (2) The packaging region was extended to include sequences of the wild-type (WT) adenovirus from 342 bp to 450 bp inclusive.
- (3) The area downstream of pIX was extended 13 nucleotides (i.e., nucleotides 3511-3523 inclusive).

These modifications (Figure 4) effectively reduced the size of the E1 deletion without overlapping with any part of the E1A/E1B gene present in the transformed PER.C6[®] cell line. All manipulations were performed by modifying the Ad shuttle vector pdeIE1sp1A.

Once the modifications were made to the shuttle vector, the changes were incorporated into the original Ad5 adenovector backbones (pAdHVO and pAdHVE3) by bacterial homologous recombination using *E. coli* BJ5183 chemically competent cells.

EXAMPLE 5

Construction of Modified Adenovector Backbones (E3+ and E3-)

The original adenovectors pAdHVO (comprising all Ad5 sequences except those nucleotides encompassing the E1 and E3 regions) and pAdHVE3 (comprising all Ad5 sequences except those nucleotides encompassing the E1 region), were each reconstructed so that they contained the modifications to the E1 region. This was accomplished by digesting the newly modified shuttle vector (MRKpdelE1 shuttle) with *PacI* and *BstZ1101* and isolating the 2,734 bp fragment which corresponds to the adenovirus sequence. This fragment was co-transformed with DNA from either *ClaI* linearized pAdHVO (E3- adenovector) or *ClaI* linearized pAdHVE3 (E3+adenovector) into *E. coli* BJ5183 competent cells. At least two colonies from each transformation were selected and grown in Terrific™ broth for 6-8 hours until turbidity was reached. DNA was extracted from each cell pellet and then transformed into *E. coli* XL1 competent cells. One colony from each transformation was selected and grown for plasmid DNA purification. The plasmid was analyzed by restriction digestions to identify correct clones. The modified adenovectors were designated MRKpAdHVO (E3- plasmid) and MRKpAdHVE3 (E3+ plasmid). Virus from these new adenovectors (MRKHVO and MRKHVE3, respectively) as well as the old version of the adenovectors were generated in the PER.C6® cell lines to accommodate the following series of viral competition experiments. In addition, the multiple cloning site of the original shuttle vector contained *ClaI* , *BamHI*, *Xho I*, *EcoRV*, *HindIII*, *Sal I*, and *Bgl II* sites. This MCS was replaced with a new MCS containing *Not I*, *Cla I*, *EcoRV* and *Asc I* sites. This new MCS has been transferred to the MRKpAdHVO and MRKpAdHVE3 pre-plasmids along with the modification made to the packaging region and *pIX* gene.

EXAMPLE 6

Analysis of the Effect of the Packaging Signal Extension

To study the effects of the modifications made to the E1 deletion region, the viruses obtained from the original backbone (pAdHVE3) and the new backbone (MRKpAdHVE3) were mixed together in equal MOI ratios (1:1 and 5:5) and passaged through several rounds; see Figure 5, Expt.#1. Both of the viruses in the experiment contained the E3 gene intact and did not contain a transgene. The only difference between the two viruses was within the region of the E1 deletion. Following the coinfection of the viruses at P1 (passage 1), the mixtures were propagated through an additional 4 passages at which time the cells were harvested

and the virus extracted and purified by CsCl banding. The viral DNA was extracted and digested with *HindIII* and the digestion products were then radioactively labeled. For the controls, the respective pre-plasmids (pAdHVE3 ("OLD E3+"); MRKpAdHVE3 ("NEW E3+")) were also digested with *HindIII* (and *PacI* to remove the vector backbone) and subsequently labeled with [³³P]dATP. The radioactively labeled digestion products were subjected to gel electrophoresis and the gel was dried down onto Whatman paper before being exposed to autoradiographic film. Figure 6 clearly shows that the new adenovirus which has the addition made to the packaging signal region has a growth advantage compared with the original adenovirus. In the experiments performed (at either ratio tested), only the digestion bands pertaining to the newly modified virus were present. The diagnostic band of size 3,206 (from the new virus) was clearly present. However, there was no evidence of the diagnostic band of size 2,737 bp expected from the original virus.

EXAMPLE 7

Analysis of the Effect of the E3 Gene

The second set of the virus competition study involved mixing equal MOI ratio (1:1) of the newly modified viruses, that obtained from MRKpAdHVO and MRKpAdHVE3 (Figure 5, Expt. #2). In this set, both viruses had the new modifications made to the E1 deletion. The first virus (that from MRKpAdHVO) does not contain an E3 gene. The second virus (that from MRKpAdHVE3) does contain the E3 gene. Neither of the viruses contain a transgene. Following co-infection of the viruses, the mixtures were propagated through an additional 4 passages at which time the cells were harvested and the total virus extracted and purified by CsCl banding. The viral DNA was extracted and digested with *HindIII* and the digestion products were then radioactively labeled. For the controls, the respective pre-plasmids MRKpAdHVO ("NEW E3-"); MRKpAdHVE3 ("NEW E3+") were also digested with *HindIII* (and *PacI* to remove the vector backbone) and then labeled with [³³P]dATP. The radioactively labeled digestion products were subjected to gel electrophoresis and the gel was dried down onto Whatman paper before being exposed to autoradiographic film. Figure 6 shows the results of the viral DNA analysis of the E3+ virus and E3- virus mixing experiment. The diagnostic band corresponding to the E3+ virus (5,665 bp) was present in greater amount compared with the diagnostic band of 3,010 bp corresponding to the E3- virus. This indicates that the virus that contains the E3 gene is able to amplify more rapidly

compared with the virus that does not contain an E3 gene. This increased amplification capacity has been confirmed by growth studies; see Table 4 below.

EXAMPLE 8

5 Construction of the new shuttle vector containing modified gag transgene –
“MRKpdelE1-CMV(no intron)-FLgag-bGHpA”

The modified plasmid pV1JnsCMV(no intron)-FLgag-bGHPA was digested with *MscI* overnight and then digested with *SfiI* for 2 hours at 50°C. The DNA was then treated with Mungbean nuclease for 30 mins at 30°C. The DNA mixture was desalted using the Qiaex II kit and then Klenow treated for 30 mins at 37°C to fully blunt the ends of the transgene fragment. The 2,559 bp transgene fragment was then gel purified. The modified shuttle vector (MRKpdeI1 shuttle) was linearized by digestion with *EcoRV*, treated with calf intestinal phosphatase and the resulting 6,479 bp fragment was then gel purified. The two purified fragments were then ligated together and several dozen clones were screened to check for insertion of the transgene within the shuttle vector. Diagnostic restriction digestion was performed to identify those clones carrying the transgene in the E1 parallel and E1 anti-parallel orientation. This strategy was followed to clone in the other gag transgenes in the MRKpdeI1 shuttle vector.

EXAMPLE 9

Construction of the MRK FG-Adenovectors

The shuttle vector containing the HIV-1 gag transgene in the E1 parallel orientation, MRKpdelE1-CMV(no intron)-FLgag-bGHpA, was digested with *Pac*I. The reaction mixture was digested with *Bsf*ZI71. The 5,291 bp fragment was purified by gel extraction. The MRKpAdHVE3 plasmid was digested with *Cla*I overnight at 37°C and gel purified. About 100 ng of the 5,290 bp shuttle +transgene fragment and ~100 ng of linearized MRKpAdHVE3 DNA were co-transformed into *E. coli* BJ5183 chemically competent cells. Several clones were selected and grown in 2 ml Terrific™ broth for 6-8 hours, until turbidity was reached. The total DNA from the cell pellet was purified using Qiagen alkaline lysis and phenol chloroform method. The DNA was precipitated with isopropanol and resuspended in 20 µl dH₂O. A 2 µl aliquot of this DNA was transformed into *E. coli* XL-1 competent cells. A single colony from each separate transformation was selected and grown overnight in 3 ml LB +100 µg/ml ampicillin. The DNA was isolated using Qiagen columns. A positive clone was identified by digestion with the restriction enzyme *Bst*EII which cleaves

within the gag gene as well as the plasmid backbone. The pre-plasmid clone is designated MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA and is 37,498 bp in size. This strategy was followed to generate E3- and E3+ versions of each of the other gag transgene constructions in both E1 parallel and E1 anti-parallel versions. Figures 7A, 7B and 7C show the various combinations of adenovectors constructed.

EXAMPLE 10

Plasmid Competition Studies

A series of plasmid competition studies was carried out. Briefly, the screening of the various combinations of new constructs was performed by mixing equal amounts of each of two competing plasmids. In the experiment shown in Figure 8A, plasmids containing the same transgene but in different orientations were mixed together to create a "competition" between the two plasmids. The aim was to look at the effects of transgene orientation. In the experiment shown in Figure 8B, plasmids containing different polyadenylation signals (but in the same orientation) were mixed together in equal amounts. The aim was to assess effects of polyA signals. Following the initial transfection, the virus was passaged through ten rounds and the viral DNA analyzed by radioactive restriction analysis.

Analysis of the viral species from the plasmid mixing experiment (Figure 8A) showed that adenovectors which had the transgene inserted in the E1 parallel orientation amplified better and were able to out-compete the adenovirus which had the transgene inserted in the E1 anti-parallel orientation. Viral DNA analysis of the mixtures at passage 3 and certainly at passage 6, showed a greater ratio of the virus carrying the transgene in the E1 parallel orientation compared with the E1 antiparallel version. By passage 10, the only viral species observed was the adenovector with the transgene in the E1 parallel orientation for both transgenes tested (hCMV(no intron)-FLgag-bGHpA and hCMV(no intron)-FLgag-SPA).

Analysis of the viral species from the plasmid mixing experiment #2 (Figure 8B) at passages 3 and 6 showed that the polyadenylation signals tested (bGHpA and SPA) did not have an effect on the growth of the virus. Even at passage 10 the two viral species in the mixture were still present in equal amounts.

EXAMPLE 11

Virus generation of an enhanced adenoviral construct – “MRK Ad5 HIV-1 gag”

The results obtained from the competition study allowed us to make the following conclusions: (1) The packaging signal extension is beneficial; (2) Presence of E3 does enhance viral growth; (3) E1 parallel orientation is recommended; and (4) PolyA signals have no effect on the growth of the adenovirus.

MRK Ad5 HIV-1 gag exhibited the most desirable results. This construct contains the hCMV(no intron)-FLgag-bGHpA transgene inserted into the new E3+ adenovector backbone, MRKpAdHVE3, in the E1 parallel orientation. We have designated this adenovector MRK Ad5 HIV-1 gag. This construct was prepared as outlined below:

The pre-plasmid MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA was digested with *PacI* to release the vector backbone and 3.3 µg was transfected by calcium phosphate method (Amersham Pharmacia Biotech.) in a 6 cm dish containing PER.C6[®] cells at ~60% confluence. Once CPE was reached (7-10 days), the culture was freeze/thawed three times and the cell debris pelleted. 1 ml of this cell lysate was used to infect into a 6 cm dish containing PER.C6[®] cells at 80-90% confluence. Once CPE was reached, the culture was freeze/thawed three times and the cell debris pelleted. The cell lysate was then used to infect a 15 cm dish containing PER.C6[®] cells at 80-90% confluence. This infection procedure was continued and expanded at passage 6. The virus was then extracted from the cell pellet by CsCl method. Two bandings were performed (3-gradient CsCl followed by a continuous CsCl gradient). Following the second banding, the virus was dialyzed in A105 buffer. Viral DNA was extracted using pronase treatment followed by phenol chloroform. The viral DNA was then digested with *HindIII* and radioactively labeled with [³³P]dATP. Following gel electrophoresis to separate the digestion products the gel was dried down on Whatman paper and then subjected to autoradiography. The digestion products were compared with the digestion products from the pre-plasmid (that had been digested with *PacI/HindIII* prior to labeling). The expected sizes were observed, indicating that the virus had been successfully rescued. This strategy was used to rescue virus from each of the various adenovector plasmid constructs prepared.

EXAMPLE 12

Stability Analyses

To determine whether the various adenovector constructs (e.g., MRK Ad5 HIV-1 gag) show genetic stability, the viruses were each passaged continually. The viral DNA was analyzed at passages 3, 6 and 10. Each virus maintained its correct genetic structure. In addition, the stability of the MRK Ad5 HIV-1 gag was analyzed under propagation conditions similar to that performed in large scale production. For this analysis, the transfections of MRK Ad5 HIV-1 gag as well as three other adenoviral vectors were repeated and the virus was purified at P3. The three other adenovectors were as follows: (1) that comprising hCMV(no intron)-Flgag with a bGHpA terminator in an E3- adenovector backbone; (2) that comprising hCMV(no intron)-Flgag with a SPA termination signal in an E3+ adenovector backbone, and that comprising a mCMV-Flgag with a bGHpA terminator in an E3+ adenovector backbone. All of the vectors have the transgene inserted in the E1 parallel orientation. Viral DNA was analyzed by radioactive restriction analysis to confirm that it was correct before being delivered to fermentation cell culture for continued passaging in serum-free media. At P5 each of the four viruses were purified and the viral DNA extracted for analysis by the restriction digestion and radiolabeling procedure. This virus has subsequently been used in a series of studies (*in vitro* gag expression in COS cells, rodent study and rhesus monkey study) as will be described below. The viruses from P5 are shown in Figure 9.

The passaging under serum-free conditions was continued for the MRKHVE3 (transgene-less, obtained from MRKpAdHVE3 pre-plasmid) and the MRKAd5HIV-1gag (obtained from MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA pre-plasmid) viruses. Figure 10 shows viral DNA analysis by radioactive restriction digestion at passage 11 for MRKHVE3, MRKAd5HIV-1gagE3-, and passage 11 and 12 for MRKAd5HIV-1gag. Aside from the first lane which is the DNA marker lane, the next three lanes are virus from the pre-plasmid controls (controls based on the original virus) - MRKpAdHVE3 (also referred to as "pMRKHVE3"), MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA, and pMRKAd5gag(E3-), respectively. As seen in Figure 10, each of the viral DNA samples show the expected bands with no extraneous bands showing. This signifies that there are no major variant adenovirus species present that can be detected by autoradiography.

Figure 11 shows the results of viral competition study between MRKHVE3 and MRKAd5HIV-1gag. These viruses were mixed together at equal MOI (140 viral

particles each; 280 vp total) at passage 6 and continued to be passaged until P11. Aside from the first lane which is the DNA marker lane, the next two lanes are the pre-plasmid controls obtained from MRKpAdHVE3 and MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA. The next two lanes are the viral DNA from the starting viral material at passage six. The last two lanes are the competition studies performed in duplicate. The data in Figure 11 shows the effect the gag transgene in culture. Growth of a MRKAd5gag virus was compared with growth of a "transgene-less" MRKHVE3. These two viruses were infected at the same MOI (i.e. 140 vp each) at passage 6 and then passaged through to passage 11 and the viral pool was analyzed by radioactive restriction analysis. The data shows that one virus did not out compete the other. Therefore, the gag transgene did not show obvious signs of toxicity to the adenovirus.

Analysis by *HindIII* digestion shows that each virus specie is present in approximately equal amounts. As above, there does not appear to be signs of any extraneous bands. Figure 12 shows higher passage numbers for MRKAd5HIV-1gag grown under serum-containing conditions. The genome integrity again has been maintained and there is no evidence of rearrangements, even at the highest passage level (P21).

Each of the four vectors shown in Figure 9 were analyzed for amplification capacity. Table 4 below shows the QPA analysis used in the estimation of viral amplification ratios at P4. The determination of the amplification ratio for the original HIV-1 gag construct is based on the clinical lot at P12. It has been shown that amplification rates increases with higher passage number for the original virus. The reason for this observation is due to the emergence of variants which exhibit increased growth rates compared to the intact adenovector. With continued passaging of the original Ad gag vector, the level of variants increases and hence amplification rates increase also.

The MRK Ad5 HIV-1 gag virus has also been continually passaged under process conditions (i.e., serum-free media). Viral DNA extracted from passages 11 and 12 show no evidence of rearrangement.

Table 4:
Amplification Ratios Based on AEX and QPA Analysis of
Virus Amplification from Passage 3 to Passage 4.

Ad gag construct	Amplification Ratio
MRKAd5gag	470
HCMV-Flgag-bGHpA [E3-]	115
HCMV-Flgag-SPA [E3+]	320
mCMV-FLgag-bGHpA [E3+]	420
Original construct *	40 - 50

* This estimation is based on the clinical lot growth characteristics at Passage 12.

EXAMPLE 13

Analytical Evaluation of the enhanced Ad5 Constructs

To study the effects of the transgene and the E3 gene on virus amplification, the enhanced adenoviral vector, MRK Ad5 HIV-1 gag, along with its transgene-less version (MRKpAdHVE3) and its E3- version (MRK Ad5 HIV-1 gag E3-), was studied for several passages under serum-free conditions. Table 5A shows the amplification ratios determined for passages P3 to P8 for MRK Ad5 HIV-1 gag. Within a certain MOI range, it has been determined that the virus output is directly proportional to the virus input. Therefore, the greater the number of virus particles per cell at infection, the greater the virus amount produced. Viral amplification ratios, on the other hand, are inversely proportional to the virus input. The lower the virus input, the greater the amplification ratio.

Table 5B shows the amplification rates of the new E3+ vector backbone MRKpAdHVE3. It has a significantly lower rate of amplification compared with the gag transgene containing version. This may be contributed to the larger size MRK Ad5 HIV-1 gag since it contains the transgene. This inclusion of the transgene brings the size of the adenovirus closer to the size of a wild type Ad5 virus. It is well known that adenoviruses amplify best when they are at close to their wild type genomic size.

Wild type Ad5 is 35,935 bp. The MRKpAdHVE3 is 32,905 bp in length. The enhanced adenovector MRK Ad5 HIV-1 gag is 35,453bp (See Figure 14 for vector map; see also Figure 15A-X show the complete pre-adenoviral vector sequence, which includes an additional 2,021 bp of the vector backbone).

- 5 Table 5C shows the amplification rates of the new E3- gag containing virus MRK Ad5 HIV-1 gag E3-. Once again, this virus shows lower growth rate than the enhanced adenoviral vector. This may be attributed to the decreased sized of this virus (due to the E3 gene deletion) compared with wild type Ad5. The MRK Ad5 HIV-1 gag E3- virus is 32,810 bp in length. This can be compared with the wild type
- 10 Ad5 which is 35,935 bp and MRK Ad5 HIV-1 gag which is 35,453 bp in length.

Table 5A: Amplification ratios determined by AEX and QPA for MRKAd5gag over several continuous passaging in serum free media. Following P5, two replicate samples were taken (rep-1 and rep-2) and analyzed.

MRKAd5gag rep1

	Xv (10 ⁶ cells/ml), Infection	Viability (%) Harvest	Harvest Time h.p.i.	Cell Passage Number	Titer 10 ⁶ vp/ml culture	Titer 10 ⁶ vp/cell	OPA 10 ⁶ TCID ₅₀ /ml	Ratio AEX/QPA	Amplification Ratio	AEX Internal Control
P4	1.49, 81%	0.58, 50%	44	46	6.7	6.9	1.72	50	470 (MOI = 125)	
P5	1.38, 93%	0.66, 47%	48	49	6.7	4.9	1.38	49	170	
P6	1.04, 94%	0.68, 77%	47	48	5.6	6.6	1.42	41	200	
P7	1.50, 94%	0.88, 61%	49.5	50	3.9	1.4	0.87	40	50	
P7	1.09, 97%	0.78, 59%	50	52	6.2	4.7	1.70	81	170	
P8	1.03, 94%	0.86, 64%	47.5	64	9.0	6.7	1.10	82	310	
P9	0.89, 95%	0.99, 73%	47.5	56	4.4	4.5	1.03	43	175	3.12
P10	1.09, 91%	1.08, 66%	47.5	59	3.0	2.6	1.16	26	100	2.84
P11	1.18, 88%	0.88, 65%	47	60	3.8	3.0	1.15	31	110	2.70
P12	0.88, 91%	0.85, 63%	47.5	47	5.4	5.5	1.20	45	200	2.60
P13	1.00, 88%	0.70, 67%	48	49	5.9	5.8	1.11	62	210	2.70
P14	1.94, 92%	0.88, 67%	46	53	6.6	4.4			160	3.18
P15	0.97, 96%	0.64, 66%	47	47	6.9	7.1			250	3.27
										3.12
										2.91

Table 5B: Amplification ratios determined by AEX and QPA for MRKHVE3 over several continuous passaging in serum free media. MRKHVE3 is the new vector backbone which does NOT carry a transgene.

MRKHVE3

	Xv (10 ⁶ cells/ml), Infection	Viability (%) Harvest	Harvest Time h.p.i.	Cell Passage Number	Titer 10 ⁶ vp/ml culture	Titer 10 ⁶ vp/cell	OPA 10 ⁶ TCID ₅₀ /ml	Ratio AEX/QPA	Amplification Ratio	AEX Internal Control
P4	1.10, 87%	1.28, 76%	49	54	4.1	3.8	1.70	25	300 (MOI = 125)	
P5	0.82, 89%	1.18, 77%	47	48	4.3	4.7	1.24	35	170	
P6	1.55, 88%	1.26, 76%	49.5	60	1.2	0.8	0.58	21	30	
P6	1.09, 97%	1.11, 81%	49	52	4.0	2.6	1.16	34	130	
P7	1.17, 91%	1.22, 81%	47.5	54	3.7	3.2	0.50	74	110	
P8	0.98, 88%	1.41, 63%	48	56	2.1	2.1	0.47	45	75	3.12
P9	1.20, 89%	1.26, 81%	47.5	58	0.8	0.7	0.29	28	25	2.84
P10	0.95, 82%	1.55, 65%	47	50	2.3	2.3	0.43	53	80	2.70
P11	1.07, 96%	1.25, 63%	48	47	2.7	2.5	0.41	66	90	2.60
P12	0.80, 91%	1.14, 60%	48.5	49	6.9	7.4	0.48	123	260	2.70
P13	1.89, 95%	1.14, 66%	45.5	53	6.8	3.0			110	3.18
P14	0.87, 96%	1.00, 88%	48.5	47	9.4	8.7			350	3.28
P15	0.87, 99%	0.87, 69%	49.5	49	6.3	6.1			218	3.27
										3.12
										2.91
										2.70
										2.52

Table 5C. Amplification ratios determined by AEX and QPA for MRKAd5gag(E3-) over several continuous passaging in serum free media. This construct is identical to the MRKAd5gag construct except that this version is DELETED of the E3 gene.

5

MRKAd5gag(E3-)

	Xv (10 ⁶ cells/ml)	Viability (%)	Harvest Time	Cell Passage	Titer	Titer	QPA	Ratio	Amplification	AEX
	Infection	Harvest	h.p.i.	Number	10 ⁶ vp/ml culture	10 ⁶ vp/cell	10 ⁶ TCID ₅₀ /ml	AEX:QPA	Ratio	Internal Control
P4	1.82, 77%	1.12, 82%	47.5	46	2.0	1.2	0.92	20	100	
P5	1.16, 82%	0.82, 43%	49	49	3.3	2.9	0.99	34	100	
P6	1.71, 86%	0.20, 10%	49	50	4.7	2.7	1.70	28	100	
P8	1.08, 97%	0.63, 64%	49.5	52	5.4	5.0	1.76	31	180	
P7	1.17, 91%	0.98, 72%	47.50	54	7.1	6.1	0.67	106	220	
P8	0.98, 88%	0.77, 48%	48	56	3.1	3.2	0.66	47	115	3.12
P9	1.20, 89%	1.03, 72%	48	58	1.8	1.5	0.57	32	55	2.84
P10	0.93, 82%	0.80, 62%	48.5	60	3.2	3.2	0.68	47	115	2.70
P11	1.07, 96%	0.88, 70%	48.5	47	5.9	5.6	0.68	87	200	2.60
P12	0.80, 81%	0.87, 59%	50	49	5.1	6.4	0.72	71	230	3.18
P13	1.96, 95%	0.81, 59%	45.5	53	7.4	3.8			135	3.28
P14	0.97, 98%	0.81, 74%	48	47	6.8	7.0			250	3.27
P15	0.87, 89%	0.84, 66%	49	49	4.8	5.5			195	3.12
										2.91
										2.78
										2.52

EXAMPLE 14

Gag Expression Analysis of the Novel Constructs

In vitro gag analysis of the MRK Ad5 HIV-1 gag and the original HIV-gag vectors (research and clinical lot) show comparable gag expression. The clinical lot shows only a slightly reduced gag expression level. The most noticeable difference is with the mCMV vector. This vector shows roughly 3 fold lower expression levels compared with the other vectors tested (which all contain hCMV promoters). The mCMV-FLgag with bGHpA assay was performed three times using different propagation and purification lots and it consistently exhibited weaker gag expression.

EXAMPLE 15

Evaluation of MRK Ad5 HIV-1 gag and Other gag-Containing Adenovectors in Balb/c Mice

Cohorts of 10 balb/c mice were vaccinated intramuscularly with escalating doses of MRK Ad5 HIV-1 gag, and the research and clinical lots of original Ad5HIV-1gag. Serum samples were collected 3 weeks post dose 1 and analyzed by anti-p24 sandwich ELISA.

Anti-p24 titers in mice that received MRK Ad5 HIV-1 gag (10⁷ and 10⁹ vp(viral particle) doses) were comparable (Figure 13) to those of the research lot of Ad5HIV-1 gag, for which much of the early rhesus data were generated on. These titers were also comparable when E3 is deleted (MRKAd5hCMVgagbGHpA(E3-)) or SPA is substituted for bGHpA terminator (MRKAd5 hCMV-gag-SPA (E3+)) or murine CMV promoter is used in place of hCMV (MRKAd5 mCMV-gag-bGHpA (E3+)) in the MRKAd5 backbone.

The results shown in Table 7 indicate that the three other vectors (in addition to the preferred vector, MRK Ad5 HIV-1 gag, are also capable of inducing strong anti-gag antibody responses in mice. Interestingly enough, while the mCMV-FLgag construct containing bGHpA and E3+ in an E1 parallel orientation showed lowest gag expression in the COS cell *in vitro* infection (Table 6) in comparison with the other vectors tested, it generated the greatest anti-gag antibody response this *in vivo* Balb/c study. Table 7 also shows a dose response in anti-gag antibody production in both the research and the clinical lot. As expected, the clinical lot shows reduced anti-gag antibody induction at each dosage level compared to the same dosage used for the research lot.

Table 6: *In vitro* analysis for gag expression in COS cells by Elisa assay.

Viral Vectors ^a	μg gag/4.8x10 ⁵ COS/10e8 parts/48hr
MRKAd5gag ^b	1.40
Clinical lot Ad5gag ^c	1.28
Research lot Ad5gag ^d	1.32
MCMVFL-gagbGHpA ^e	0.42

^a A_{260nm} absorbance readings taken for viral particle determinations.

^b MRKAd5gag was produced in serum free conditions and purified at P5.

^c Clinical lot# Ad5gagFN0001

^d Research Ad5FLgag lot# 6399

^e mCMVFL-gagbGHpA was produced in serum free conditions and purified at P5.

Table 7: mHIV020 Anti-p24 Ab Titers in Balb/c mice (n=10) vaccinated with various Adgag constructs and lots (3 week post dose1).

Group ID	Vaccine	Dose (vp)	GMT	SE upper	SE lower
1	^a MRKAd5gag	10 ⁷	25600	5877	4780
2	"	10 ⁹	409600	94028	76473
3	hCMV FL-gag bGHpA [E3-] →	10 ⁷	7352	2077	1620
4	"	10 ⁹	235253	59767	47659
5	hCMV FL-gag SPA [E3+] →	10 ⁷	12800	9905	236
6	"	10 ⁹	310419	99181	75165
7	^b mCMV FL-gag bGHpA [E3+] →	10 ⁷	44572	23504	15389
8	"	10 ⁹	941014	239068	190836
9	^c hCMV FL-gag bGHpA [E3-] ←	10 ⁷	3676	934	745
10	"	10 ⁹	117627	17491	15227
11	research lot hCMV intronA FL-gag bGHpA [E3-] <-	10 ⁶	528	262	175
12	"	10 ⁷	14703	5274	3882
13	"	10 ⁸	58813	14942	11915
14	"	10 ⁹	204800	53232	42250
15	clinical lot hCMVintronA FL-gag bGHpA [E3-] <-	10 ⁶	230	82	61
16	"	10 ⁷	4222	3405	1138
17	"	10 ⁸	19401	3939	3274
18	"	10 ⁹	89144	25187	19639
19	Naïve	none	93	7	6

*2x50 µL i.m. (quad) injections/animal

†i.s: Youil, Chen, Casimiro

Vaccination: T. Toner, Q. Su

Assay: M. Chen

^aThe structure of MRKAd5gag is: hCMVFL-gagbGHpA [E3+] → The same lot of MRKAd5gag used in this rodent study was used in the Rhesus monkey study (Tables 7 and 8).

^bThe same lot of mCMVFL-gagbGHpA[E3+] used in the *in vitro* study (Table 6) was used here.

^cThis construct was designed by Volker Sandig. It contains a shorter version of the hCMV promoter than that used in the MRK constructs. The adenovector backbone is identical to the original backbone used in the original Adgag vector. Expression at 10⁶ dose from this vector is 7 fold lower than the same dose of the MRKAd5gag and 4 fold lower than the research lot.

EXAMPLE 16

Comparison of Humoral and Cellular Responses Towards the Original Ad-gag

Construct with the New MRK Ad5 HIV-1 gag in Rhesus Monkeys

- 5 Cohorts of 3 rhesus monkeys were vaccinated intramuscularly with MRK Ad5 HIV-1 gag or the clinical Ad5gag bulk at two doses, 10¹¹ vp and 10⁹ vp. Immunizations were conducted at week 0, 4, and 25. Serum and PBMC samples were collected at selected time points. The serum sample were assayed for anti-p24 Ab titers (using competitive based assay) and the PBMCs for antigen-specific IFN-
10 gamma secretion following overnight stimulation with gag 20-mer peptide pool (via ELISpot assay).

The results shown in Table 8 indicate comparable responses with respect to the generation of anti-gag antibodies. The frequencies of gag-specific T cells in

- peripheral blood assmumarized in Table 9 demonstrate a strong cellular immune response generated after a single dose with the new construct MRK Ad5 HIV-1 gag. The responses are also boostable with second dose of the same vector. The vector is also able to induce CD8+ T cell responses (as evident by remaining spot counts after
- 5 CD4+ depletion of PBMCs) which are responsible for cytotoxic activity.

Table 8 Anti-p24 antibody titers (in mMU/mL) in rhesus macaques immunized with gag-expressing adenovectors (Protocol HIV203).

Vaccine	Pre	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 25	Wk 28
MR KAd5gag ^a , 10 ¹¹ vp								
97N010	<10	118	5528	11523	7062	21997	ND	51593
97N116	<10	62	772	1447	1562	2174	ND	20029
98X007	<10	66	3353	6156	6845	3719	ND	24031
MR KAd5gag, 10 ⁹ vp								
97N120	<10	51	204	318	366	482	ND	6550
97N144	<10	18	118	274	706	888	ND	7136
98X008	<10	15	444	386	996	1072	ND	12851
Ad5gag ^b , Clinical Lot, 10 ¹¹ vp								
97X001	<10	87	2579	4718	7174	7250	ND	69226
97N146	<10	72	3604	7380	7526	18906	ND	60283
98X009	<10	78	4183	3946	3124	6956	ND	26226
Ad5gag, Clinical Lot, 10 ⁹ vp								
97N020	<10	<10	143	371	390	1821	ND	17177
97X003	<10	<10	39	93	156	596	ND	2053
98X012	<10	81	342	717	956	1558	ND	11861
MR KAd5gag (hCMV, bGHpA, E3+)								
^a original Ad5gag vector (hCMV/Intron A, bGHpA, E3-), lot#FN0001								
ND, not determined								

Table 9. Number of gag-specific T cells per million peripheral blood mononuclear cells (PBMCs) in rhesus monkeys immunized with gag-expressing adenovectors. Also included are those frequencies in PBMCs depleted of CD4⁺ T cells.

Grp #	Vaccination T=0,4,25 wks	Monkey ID	T=4 Wk		T=6 Wk		T=11 Wk		T=16 Wk		T=25 Wk		T=28 Wk	
			Media ^a	Gag H ^b	Media	Gag H	Media	Gag H	Media	Gag H	Media	Gag H	Media	Gag H
1	MRKAd5gag 10 ⁹ vp	97ND10	6	89	0	395	0	1058	0	1174	3	775	4	1074
		97ND10(CD4-)	4	38			3	993			0	76	0	594
		97N116	1	388	1	609	0	534	4	395	1	261	0	408
		97N116(CD4-)	11	676			0	593			0	184	0	666
		98X007	10	579	0	1304	3	2193	1	2118	3	1588	0	2113
		98X007(CD4-)	20	965			0	2675			0	1656	0	1278
2	MRKAd5gag 10 ⁹ vp	97N120	5	275	1	249	4	141	4	119	9	206	4	219
		97N120(CD4-)	11	170			0	85			0	75	1	219
		97N144	3	236	6	438	1	318	3	256	1	98	5	373
		97N144(CD4-)	6	148			0	285			ND	ND	0	625
		98X008	4	368	1	1090	3	891	4	673	3	473	5	735
		98X008(CD4-)	14	696			0	1175			0	391	4	848
3	Ad5gag clinical lot 10 ¹¹ vp	97X001	0	281	1	485	0	817	0	1220	1	894	0	1858
		97X001(CD4-)	10	283			3	996			0	1010	0	1123
		97N146	3	150	1	485	0	339	1	1272	3	1238	3	1785
		97N146(CD4-)	6	133			0	370			0	654	0	971
		98X009	0	93	3	339	3	559	0	896	1	384	0	1748
		98X009(CD4-)	0	73			0	333			0	225	0	644
4	Ad5gag clinical lot 10 ⁹ vp	97ND20	3	30	1	101	0	66	0	36	0	26	0	41
		97ND20(CD4-)	10	29			0	15			0	1	0	16
		97X003	4	68	8	134	0	18	1	38	4	38	6	81
		97X003(CD4-)	9	40			0	6			0	4	0	19
		98X012	5	85	3	54	1	34	0	18	0	20	1	121
		98X012(CD4-)	11	70			0	11			0	8	0	41
5	Native	96R041	6	8	1	1	0	0	0	0	0	0	1	0
		053F	14	18	5	16	20	14	19	15	10	15	24	9

^aBased on either 4x10⁶ or 2x10⁶ cells per well (depending on spot density)

^b... determined

^cMock or no peptide control

^dPool of 20-aa peptides overlapping by 10 aa and encompassing the gag sequence

5

The adenovectors described herein and, particularly, MRK Ad5 HIV-1 gag, represent very promising HIV-gag adenovectors with respect to their enhanced growth characteristics in both serum and, more importantly, in serum-free media conditions. In comparison with the current HIV-1 gag adenovector construct, MRK Ad5 HIV-1 gag shows a 5-10 fold increased amplification rate. We have shown that it is genetically stable at passage 21. This construct is able to generate significant cellular immune responses *in vivo* even at a relatively low dose of 10⁹ vp. The potency of the MRKAd5gag construct is comparable to, if not better than the original HIV-1gag vector as shown in this rhesus monkey study.

15

EXAMPLE 17

CODON OPTIMIZED HIV-1 POL AND CODON OPTIMIZED HIV-1 POL MODIFICATIONS

20

The open reading frames for the various synthetic *pol* genes disclosed herein comprise coding sequences for the reverse transcriptase (or RT which consists of a polymerase and RNase H activity) and integrase (IN). The protein sequence is based

on that of Hxb2r, a clonal isolate of IIIB; this sequence has been shown to be closest to the consensus clade B sequence with only 16 nonidentical residues out of 848 (Korber, et al., 1998, Human retroviruses and AIDS, Los Alamos National Laboratory, Los Alamos, New Mexico). The skilled artisan will understand after
 5 review of this specification that any available HIV-1 or HIV-2 strain provides a potential template for the generation of HIV pol DNA vaccine constructs disclosed herein. It is further noted that the protease gene is excluded from the DNA vaccine constructs of the present invention to insure safety from any residual protease activity in spite of mutational inactivation. The design of the gene sequences for both wild-
 10 type (wt-pol) and inactivated pol (IA-pol) incorporates the use of human preferred ("humanized") codons for each amino acid residue in the sequence in order to maximize *in vivo* mammalian expression (Lathe, 1985, *J. Mol. Biol.* 183:1-12). As can be discerned by inspecting the codon usage in SEQ ID NOs: 1, 3, 5 and 7, the following codon usage for mammalian optimization is preferred: Met (ATG), Gly
 15 (GGC), Lys (AAG), Trp (TGG), Ser (TCC), Arg (AGG), Val (GTG), Pro (CCC), Thr (ACC), Glu (GAG); Leu (CTG), His (CAC), Ile (ATC), Asn (AAC), Cys (TGC), Ala (GCC), Gln (CAG), Phe (TTC) and Tyr (TAC). For an additional discussion relating to mammalian (human) codon optimization, see WO 97/31115 (PCT/US97/02294), which, as noted elsewhere in this specification, is hereby incorporated by reference. It
 20 is intended that the skilled artisan may use alternative versions of codon optimization or may omit this step when generating HIV pol vaccine constructs within the scope of the present invention. Therefore, the present invention also relates to non-codon optimized versions of DNA molecules and associated recombinant adenoviral HIV vaccines which encode the various wild type and modified forms of the HIV Pol
 25 protein disclosed herein. However, codon optimization of these constructs is a preferred embodiment of this invention.

A particular embodiment of this portion of the invention comprises codon optimized nucleotide sequences which encode wt-pol DNA constructs (herein, "wt-pol" or "wt-pol (codon optimized)") wherein DNA sequences encoding the protease
 30 (PR) activity are deleted, leaving codon optimized "wild type" sequences which encode RT (reverse transcriptase and RNase H activity) and IN integrase activity. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:1, the open reading frame being contained from an initiating Met residue at nucleotides 10-12 to a termination codon from nucleotides 2560-2562. SEQ ID NO:1 is as follows:
 35 AGATCTACCA TGGCCCCCAT CTCCCCATT GAGACTGTGC CTGTGAAGCT GAAGCCTGGC
 ATGGATGGCC CCAAGGTGAA GCAGTGGCCC CTGACTGAGG AGAAGATCAA GGCCCTGGTG

GAAATCTGCA CTGAGATGGA GAAGGAGGGC AAAATCTCCA AGATTGGCCC CGAGAACCCC
 TACAACACCC CTGTGTTTGC CATCAAGAAG AAGGACTCCA CCAAGTGGAG GAAGCTGGTG
 GACTTCAGGG AGCTGAACAA GAGGACCCAG GACTTCTGGG AGGTGCAGCT GGGCATCCCC
 CACCCCGCTG GCCTGAAGAA GAAGAAGTCT GTGACTGTGC TGGATGTGGG GGATGCCTAC
 5 TTCTCTGTGC CCCTGGATGA GGACTTCAGG AAGTACACTG CCTTCACCAT CCCCTCCATC
 AACAAATGAGA CCCCTGGCAT CAGGTACCAG TACAATGTGC TGCCCCAGGG CTGGAAGGGC
 TCCCCTGCCA TCTTCCAGTC CTCCATGACC AAGATCCTGG AGCCCTTCAG GAAGCAGAAC
 CCTGACATTG TGATCTACCA GTACATGGAT GACCTGTATG TGGGCTCTGA CCTGGAGATT
 GGGCAGCACA GGACCAAGAT TGAGGAGCTG AGGCAGCACC TGCTGAGGTG GGGCCTGACC
 10 ACCCCTGACA AGAAGCACCA GAAGGAGCCC CCCTTCCTGT GGATGGGCTA TGAGCTGCAC
 CCCGACAAGT GGACTGTGCA GCCCATTGTG CTGCCCTGAGA AGGACTCCTG GACTGTGAAT
 GACATCCAGA AGCTGGTGGG CAAGCTGAAC TGGGCCTCCC AAATCTACCC TGGCATCAAG
 GTGAGGCAGC TGTGCAAGCT GCTGAGGGGC ACCAAGGCCC TGACTGAGGT GATCCCCCTG
 ACTGAGGAGG CTGAGCTGGA GCTGGCTGAG AACAGGGAGA TCCTGAAGGA GCCTGTGCAT
 15 GGGGTGTACT ATGACCCCTC CAAGGACCTG ATTGCTGAGA TCCAGAAGCA GGGCCAGGGC
 CAGTGGACCT ACCAAATCTA CCAGGAGCCC TTCAAGAACC TGAAGACTGG CAAGTATGCC
 AGSATGAGGG GGGCCACAC CAATGATGTG AAGCAGCTGA CTGAGGCTGT GCAGAAGATC
 ACCACTGAGT CCATTGTGAT CTGGGGCAAG ACCCCCAAGT TCAAGCTGCC CATCCAGAAG
 GAGACCTGGG AGACCTGGTG GACTGAGTAC TGGCAGGCCA CCTGGATCCC TGAGTGGGAG
 20 TTTGTGAACA CCCCCCCCCT GGTGAAGCTG TGGTACCAGC TGGAGAAGGA GCCCATTGTG
 GGGGCTGAGA CCTTCTATGT GGATGGGGCT GCCAACAGGG AGACCAAGCT GGGCAAGGCT
 GGCTATGTGA CCAACAGGGG CAGGCAGAAG GTGGTGACCC TGACTGACAC CACCAACCAG
 AAGACTGAGC TCCAGGCCAT CTACCTGGCC CTCCAGGACT CTGGCCTGGA GGTGAACATT
 GTGACTGACT CCCAGTATGC CCTGGGCATC ATCCAGGCCC AGCCTGATCA GTCTGAGTCT
 25 GAGCTGGTGA ACCAGATCAT TGAGCAGCTG ATCAAGAAGG AGAAGGTGTA CCTGGCCTGG
 GTGCCTGCCC ACAAGGGCAT TGGGGGCAAT GAGCAGGTGG ACAAGCTGGT GTCTGCTGGC
 ATCAGGAAGG TGCTGTTTCT GGATGGCATT GACAAGGCCC AGGATGAGCA TGAGAAGTAC
 CACTCCAACCT GGAGGGCTAT GGCTCTGAC TTCAACCTGC CCCCTGTGGT GGCTAAGGAG
 ATTGTGGCCT CCTGTGACAA GTGCCAGCTG AAGGGGAGG CCATGCATGG GCAGGTGGAC
 30 TGCTCCCTTG GCATCTGGCA GCTGGACTGC ACCACCTGG AGGGCAAGGT GATCCTGGTG
 GCTGTGCATG TGGCCTCCGG CTACATTGAG GCTGAGGTGA TCCCTGCTGA GACAGGCCAG
 GAGACTGCCT ACTTCCTGCT GAAGCTGGCT GGCAGGTGGC CTGTGAAGAC CATCCACACT
 GACAATGGCT CCAACTTCAC TGGGGCCACA GTGAGGGCTG CCTGCTGGTG GGCTGGCATC
 AAGCAGGAGT TTGGCATCCC CTACAACCCC CAGTCCCAGG GGGTGGTGGA GTCCATGAAC
 35 AAGGAGCTGA AGAAGATCAT TGGGCAGGTG AGGGACCAGG CTGAGCACCT GAAGACAGCT
 GTGCAGATGG CTGTGTTTCAT CCACAACCTC AAGAGGAAGG GGGGCATCGG GGGCTACTCC

GCTGGGGAGA GGATTGTGGA CATCATTGCC ACAGACATCC AGACCAAGGA GCTCCAGAAG
 CAGATCACCA AGATCCAGAA CTTCAGGGTG TACTACAGGG ACTCCAGGAA CCCCCTGTGG
 AAGGGCCCTG CCAAGCTGCT GTGGAAGGGG GAGGGGGCTG TGGTGATCCA GGACAACTCT
 GACATCAAGG TGGTGCCCAG GAGGAAGGCC AAGATCATCA GGGACTATGG CAAGCAGATG
 5 GCTGGGGATG ACTGTGTGGC CTCCAGGCAG GATGAGGACT AAAGCCCGGG CAGATCT (SEQ
 ID NO:1).

The open reading frame of the wild type pol construct disclosed as SEQ ID
 NO:1 contains 850 amino acids, disclosed herein as SEQ ID NO:2, as follows:

Met Ala Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro
 10 Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys
 Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys
 Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala
 Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg
 Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile
 15 Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Asp
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys
 Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile
 Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala
 Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln
 20 Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val Gly
 Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu Arg
 Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His Gln
 Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys
 Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
 25 Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile
 Tyr Pro Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr
 Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu
 Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr
 Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln
 30 Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys
 Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys
 Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile
 Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
 Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp
 35 Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu
 Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Asp Gly Ala Ala

Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly
 Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Glu
 Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn
 Ile Val Thr Asp Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro
 5 Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile
 Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
 Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys
 Val Leu Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys
 Tyr His Ser Asn Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro
 10 Val Val Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys
 Gly Glu Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln
 Leu Asp Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His
 Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly
 Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val
 15 Lys Thr Ile His Thr Asp Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
 Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro
 Tyr Asn Pro Gln Ser Gln Gly Val Val Glu Ser Met Asn Lys Glu Leu
 Lys Lys Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr
 Ala Val Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly
 20 Ile Gly Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr
 Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn
 Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu Trp Lys Gly Pro
 Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn
 Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
 25 Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp
 Glu Asp (SEQ ID NO:2).

The present invention especially relates to an adenoviral vector vaccine which
 comprises a codon optimized HIV-1 DNA pol construct wherein, in addition to
 deletion of the portion of the wild type sequence encoding the protease activity, a
 30 combination of active site residue mutations are introduced which are deleterious to
 HIV-1 pol (RT-RH-IN) activity of the expressed protein. Therefore, the present
 invention preferably relates to an adenoviral HIV-1 DNA pol-based vaccine wherein
 the construct is devoid of DNA sequences encoding any PR activity, as well as
 containing a mutation(s) which at least partially, and preferably substantially,
 35 abolishes RT, RNase and/or IN activity. One type of HIV-1 pol mutant which is part
 and parcel of an adenoviral vector vaccine may include but is not limited to a mutated

DNA molecule comprising at least one nucleotide substitution which results in a point mutation which effectively alters an active site within the RT, RNase and/or IN regions of the expressed protein, resulting in at least substantially decreased enzymatic activity for the RT, RNase H and/or IN functions of HIV-1 Pol. In a preferred embodiment of this portion of the invention, a HIV-1 DNA pol construct contains a mutation or mutations within the Pol coding region which effectively abolishes RT, RNase H and IN activity. An especially preferable HIV-1 DNA pol construct in a DNA molecule which contains at least one point mutation which alters the active site of the RT, RNase H and IN domains of Pol, such that each activity is at least substantially abolished. Such a HIV-1 Pol mutant will most likely comprise at least one point mutation in or around each catalytic domain responsible for RT, RNase H and IN activity, respectfully. To this end, an especially preferred HIV-1 DNA pol construct is exemplified herein and contains nine codon substitution mutations which results in an inactivated Pol protein (IA Pol: SEQ ID NO:4, Figure 17A-C) which has no PR, RT, RNase or IN activity, wherein three such point mutations reside within each of the RT, RNase and IN catalytic domains. Therefore, an especially preferred exemplification is an adenoviral vaccine which comprises, in an appropriate fashion, a DNA molecule which encodes IA-pol, which contains all nine mutations as shown below in Table 1. An additional preferred amino acid residue for substitution is Asp551, localized within the RNase domain of Pol. Any combination of the mutations disclosed herein may suitable and therefore may be utilized as an IA-Pol-based vaccine of the present invention. While addition and deletion mutations are contemplated and within the scope of the invention, the preferred mutation is a point mutation resulting in a substitution of the wild type amino acid with an alternative amino acid residue.

Table 1

	<u>wt aa</u>	<u>aa residue</u>	<u>mutant aa</u>	<u>enzyme function</u>
	Asp	112	Ala	RT
	Asp	187	Ala	RT
30	Asp	188	Ala	RT
	Asp	445	Ala	RNase H
	Glu	480	Ala	RNase H
	Asp	500	Ala	RNase H
	Asp	626	Ala	IN
35	Asp	678	Ala	IN
	Glu	714	Ala	IN

It is preferred that point mutations be incorporated into the IApol mutant adenoviral vaccines of the present invention so as to lessen the possibility of altering epitopes in and around the active site(s) of HIV-1 Pol.

To this end, SEQ ID NO:3 discloses the nucleotide sequence which codes for a codon optimized pol in addition to the nine mutations shown in Table 1, disclosed as follows, and referred to herein as "IApol":

5 AGATCTACCA TGGCCCCCAT CTCCCCATT GAGACTGTGC CTGTGAAGCT GAAGCCTGGC
 ATGGATGGCC CCAAGGTGAA GCAGTGGCCC CTGACTGAGG AGAAGATCAA GGCCCTGGTG
 GAAATCTGCA CTGAGATGGA GAAGGAGGGC AAAATCTCCA AGATTGGCCC CGAGAACCCC
 10 TACAACACCC CTGTGTTTGC CATCAAGAAG AAGGACTCCA CCAAGTGGAG GAAGCTGGTG
 GACTTCAGGG AGCTGAACAA GAGGACCCAG GACTTCTGGG AGGTGCAGCT GGGCATCCCC
 CACCCCGCTG GCCTGAAGAA GAAGAAGTCT GTGACTGTGC TGGCTGTGGG GGATGCCTAC
 TTCTCTGTGC CCCTGGATGA GGACTTCAGG AAGTACACTG CCTTEACCAT CCCCTCCATC
 AACAAATGAGA CCCCTGGCAT CAGGTACCAG TACAATGTGC TGCCCCAGGG CTGGAAGGGC
 15 TCCCCTGCCA TCTTCAGTC CTCCATGACC AAGATCCTGG AGCCCTTCAG GAAGCAGAAC
 CCTGACATTG TGATCTACCA GTACATGGCT GCCCTGTATG TGGGCTCTGA CCTGGAGATT
 TGGCAGCACA GGACCAAGAT TGAGGAGCTG AGGCAGCACC TGCTGAGGTG GGGCCTGACC
 ACCCCTGACA AGAAGCACCA GAAGGAGCCC CCCTTCCTGT GGATGGGCTA TGAGCTGCAC
 CCCGACAAGT GGACTGTGCA GCCCATTTGTG CTGCCTGAGA AGGACTCCTG GACTGTGAAT
 20 GACATCCAGA AGCTGGTGGG CAAGCTGAAC TGGGCCTCCC AAATCTACCC TGGCATCAAG
 GTGAGGCAGC TGTGCAAGCT GCTGAGGGGC ACCAAGGCCC TGACTGAGGT GATCCCCCTG
 ACTGAGGAGG CTGAGCTGGA GCTGGCTGAG AACAGGGAGA TCCTGAAGGA GCCTGTGCAT
 GGGGTGTACT ATGACCCCTC CAAGGACCTG ATTGCTGAGA TCCAGAAGCA GGGCCAGGGC
 CAGTGGACCT ACCAAATCTA CCAGGAGCCC TTCAAGAACC TGAAGACTGG CAAGTATGCC
 25 AGGATGAGGG GGGCCACAC CAATGATGTG AAGCAGCTGA CTGAGGCTGT GCAGAAGATC
 ACCACTGAGT CCATTGTGAT CTGGGGCAAG ACCCCCAAGT TCAAGCTGCC CATCCAGAAG
 GAGACCTGGG AGACCTGGTG GACTGAGTAC TGGCAGGCCA CCTGGATCCC TGAGTGGGAG
 TTTGTGAACA CCCCCCCCCT GGTGAAGCTG TGGTACCAGC TGGAGAAGGA GCCCATTGTG
 GGGGCTGAGA CCTTCTATGT GGCTGGGGCT GCCAACAGGG AGACCAAGCT GGGCAAGGCT
 30 GGCTATGTGA CCAACAGGGG CAGGCAGAAG GTGGTGACCC TGACTGACAC CACCAACCAG
 AAGACTGCCC TCCAGGCCAT CTACCTGGCC CTCCAGGACT CTGGCCTGGA GGTGAACATT
 GTGACTGCCT CCCAGTATGC CCTGGGCATC ATCCAGGCCC AGCCTGATCA GTCTGAGTCT
 GAGCTGGTGA ACCAGATCAT TGAGCAGCTG ATCAAGAAGG AGAAGGTGTA CCTGGCCTGG
 GTGCCTGCCC ACAAGGGCAT TGGGGGCAAT GAGCAGGTGG ACAAGCTGGT GTCTGCTGGC
 35 ATCAGGAAGG TGCTGTTTCT GGATGGCATT GACAAGGCCC AGGATGAGCA TGAGAAGTAC
 CACTCCAACCT GGAGGGCTAT GGCCTCTGAC TTCAACCTGC CCCCTGTGGT GGCTAAGGAG

ATTGTGGCCT CCTGTGACAA GTGCCAGCTG AAGGGGGAGG CCATGCATGG GCAGGTGGAC
 TGCTCCCCCTG GCATCTGGCA GCTGGCCTGC ACCCACCTGG AGGGCAAGGT GATCCTGGTG
 GCTGTGCATG TGGCCTCCGG CTACATTGAG GCTGAGGTGA TCCCTGCTGA GACAGGCCAG
 GAGACTGCCT ACTTCCTGCT GAAGCTGGCT GGCAGGTGGC CTGTGAAGAC CATCCACACT
 5 GCCAATGGCT CCAACTTCAC TGGGGCCACA GTGAGGGCTG CCTGCTGGTG GGCTGGCATC
 AAGCAGGAGT TTGGCATCCC CTACAACCCC CAGTCCCAGG GGGTGGTGGC CTCCATGAAC
 AAGGAGCTGA AGAAGATCAT TGGGCAGGTG AGGGACCAGG CTGAGCACCT GAAGACAGCT
 GTGCAGATGG CTGTGTTTAT CCACAATTTC AAGAGGAAGG GGGGCATCGG GGGCTACTCC
 GCTGGGGAGA GGATTGTGGA CATCATTGCC ACAGACATCC AGACCAAGGA GCTCCAGAAG
 10 CAGATCACCA AGATCCAGAA CTTCAGGGTG TACTACAGGG ACTCCAGGAA CCCCCTGTGG
 AAGGGCCCTG CCAAGCTGCT GTGGAAGGGG GAGGGGGCTG TGGTGATCCA GGACAATCT
 GACATCAAGG TGGTGCCAG GAGGAAGGCC AAGATCATCA GGGACTATGG CAAGCAGATG
 GCTGGGGATG ACTGTGTGGC CTCCAGGCAG GATGAGGACT AAAGCCCGGG CAGATCT (SEQ ID
 NO:3) .

15 In order to produce the IA-pol-based adenoviral vaccines of the present
 invention, inactivation of the enzymatic functions was achieved by replacing a total of
 nine active site residues from the enzyme subunits with alanine side-chains. As
 shown in Table 1, all residues that comprise the catalytic triad of the polymerase,
 namely Asp112, Asp187, and Asp188, were substituted with alanine (Ala) residues
 20 (Larder, et al., *Nature* 1987, 327: 716-717; Larder, et al., 1989, *Proc. Natl. Acad. Sci.*
 1989, 86: 4803-4807). Three additional mutations were introduced at Asp445,
 Glu480 and Asp500 to abolish RNase H activity (Asp551 was left unchanged in this
 IA Pol construct), with each residue being substituted for an Ala residue, respectively
 (Davies, et al., 1991, *Science* 252:, 88-95; Schatz, et al., 1989, *FEBS Lett.* 257: 311-
 25 314; Mizrahi, et al., 1990, *Nucl. Acids. Res.* 18: pp. 5359-5353). HIV pol integrase
 function was abolished through three mutations at Asp626, Asp678 and Glu714.
 Again, each of these residues has been substituted with an Ala residue (Wiskerchen,
 et al., 1995, *J. Virol.* 69: 376-386; Leavitt, et al., 1993, *J. Biol. Chem.* 268: 2113-
 2119). Amino acid residue Pro3 of SEQ ID NO:4 marks the start of the RT gene.
 30 The complete amino acid sequence of IA-Pol is disclosed herein as SEQ ID NO:4 and
 Figure 17A-C, as follows:

Met Ala Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro
 Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys
 Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys
 35 Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala
 Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg

Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile
 Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Ala
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys
 Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile
 5 Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala
 Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln
 Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Ala Ala Leu Tyr Val Gly
 Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu Arg
 Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His Gln
 10 Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys
 Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
 Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile
 Tyr Pro Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr
 Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu
 15 Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr
 Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln
 Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys
 Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys
 Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile
 20 Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
 Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp
 Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu
 Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Ala Gly Ala Ala
 Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly
 25 Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Ala
 Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn
 Ile Val Thr Ala Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro
 Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile
 Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
 30 Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys
 Val Leu Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys
 Tyr His Ser Asn Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro
 Val Val Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys
 Gly Glu Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln
 35 Leu Ala Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His
 Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly

Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val
 Lys Thr Ile His Thr Ala Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
 Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro
 Tyr Asn Pro Gln Ser Gln Gly Val Val Ala Ser Met Asn Lys Glu Leu
 5 Lys Lys Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr
 Ala Val Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly
 Ile Gly Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr
 Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn
 Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu Trp Lys Gly Pro
 10 Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn
 Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
 Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp
 Glu Asp (SEQ ID NO:4).

As noted above, it will be understood that any combination of the mutations
 15 disclosed above may be suitable and therefore be utilized as an IA-pol-based
 adenoviral HIV vaccine of the present invention, either when administered alone or in
 a combined modality regime and/or a prime-boost regimen. For example, it may be
 possible to mutate only 2 of the 3 residues within the respective reverse transcriptase,
 RNase-H, and integrase coding regions while still abolishing these enzymatic
 20 activities. However, the IA-pol construct described above and disclosed as SEQ ID
 NO:3, as well as the expressed protein (SEQ ID NO:4;) is preferred. It is also
 preferred that at least one mutation be present in each of the three catalytic domains.

Another aspect of this portion of the invention are codon optimized HIV-1
 Pol-based vaccine constructions which comprise a eukaryotic trafficking signal
 25 peptide such as from tPA (tissue-type plasminogen activator) or by a leader peptide
 such as is found in highly expressed mammalian proteins such as immunoglobulin
 leader peptides. Any functional leader peptide may be tested for efficacy. However,
 a preferred embodiment of the present invention, as with HIV-1 Nef constructs shown
 herein, is to provide for a HIV-1 Pol mutant adenoviral vaccine construction wherein
 30 the pol coding region or a portion thereof is operatively linked to a leader peptide,
 preferably a leader peptide from human tPA. In other words, a codon optimized
 HIV-1 Pol mutant such as IA-Pol (SEQ ID NO:4) may also comprise a leader peptide
 at the amino terminal portion of the protein, which may effect cellular trafficking and
 hence, immunogenicity of the expressed protein within the host cell. As noted in
 35 Figure 16A-B, a DNA vector which may be utilized to practice the present invention
 may be modified by known recombinant DNA methodology to contain a leader signal

peptide of interest, such that downstream cloning of the modified HIV-1 protein of interest results in a nucleotide sequence which encodes a modified HIV-1 tPA/Pol protein. In the alternative, as noted above, insertion of a nucleotide sequence which encodes a leader peptide may be inserted into a DNA vector housing the open reading frame for the Pol protein of interest. Regardless of the cloning strategy, the end result is a polynucleotide vaccine which comprises vector components for effective gene expression in conjunction with nucleotide sequences which encode a modified HIV-1 Pol protein of interest, including but not limited to a HIV-1 Pol protein which contains a leader peptide. The amino acid sequence of the human tPA leader utilized herein is as follows: MDAMKRGGLCCVLLLCGAVFVSPSEISS (SEQ ID NO:17). Therefore, another aspect of the present invention is to generate HIV-1 Pol-based vaccine constructions which comprise a eukaryotic trafficking signal peptide such as from tPA. To this end, the present invention relates to a DNA molecule which encodes a codon optimized wt-pol DNA construct wherein the protease (PR) activity is deleted and a human tPA leader sequence is fused to the 5' end of the coding region. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:5, the open reading frame disclosed herein as SEQ ID NO:6.

To this end, the present invention relates to a DNA molecule which encodes a codon optimized wt-pol DNA construct wherein the protease (PR) activity is deleted and a human tPA leader sequence is fused to the 5' end of the coding region (herein, "tPA-wt-pol"). A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:5, the open reading frame being contained from an initiating Met residue at nucleotides 8-10 to a termination codon from nucleotides 2633-2635. SEQ ID NO:5 is as follows:

25 GATCACCATG GATGCAATGA AGAGAGGGCT CTGCTGTGTG CTGCTGCTGT GTGGAGCAGT
CTTCGTTTCG CCCAGCGAGA TCTCCGCCCC CATCTCCCCC ATTGAGACTG TGCCTGTGAA
GCTGAAGCCT GGCATGGATG GCCCCAAGGT GAAGCAGTGG CCCCTGACTG AGGAGAAGAT
CAAGGCCCTG GTGGAAATCT GCACTGAGAT GGAGAAGGAG GGCAAAATCT CCAAGATTGG
CCCCGAGAAC CCCTACAACA CCCCTGTGTT TGCCATCAAG AAGAAGGACT CCACCAAGTG
30 GAGGAAGCTG GTGGACTTCA GGGAGCTGAA CAAGAGGACC CAGGACTTCT GGGAGGTGCA
GCTGGGCATC CCCCACCCCG CTGGCCTGAA GAAGAAGAAG TCTGTGACTG TGCTGGATGT
GGGGGATGCC TACTTCTCTG TGCCCCTGGA TGAGGACTTC AGGAAGTACA CTGCCCTCAC
CATCCCCTCC ATCAACAATG AGACCCCTGG CATCAGGTAC CAGTACAATG TGCTGCCCCA
GGGCTGGAAG GGCTCCCCTG CCATCTTCCA GTCCTCCATG ACCAAGATCC TGGAGCCCTT
35 CAGGAAGCAG AACCCTGACA TTGTGATCTA CCAGTACATG GATGACCTGT ATGTGGGCTC
TGACCTGGAG ATTGGGCAGC ACAGGACCAA GATTGAGGAG CTGAGGCAGC ACCTGCTGAG

GTGGGGCCTG ACCACCCCTG ACAAGAAGCA CCAGAAGGAG CCCCCCTTCC TGTGGATGGG
 CTATGAGCTG CACCCCGACA AGTGGACTGT GCAGCCCAT TGTGCTGCCTG AGAAGGACTC
 CTGGACTGTG AATGACATCC AGAAGCTGGT GGGCAAGCTG AACTGGGCCT CCCAAATCTA
 CCCTGGCATC AAGGTGAGGC AGCTGTGCAA GCTGCTGAGG GGCACCAAGG CCCTGACTGA
 5 GGTGATCCCC CTGACTGAGG AGGCTGAGCT GGAGCTGGCT GAGAACAGGG AGATCCTGAA
 GGAGCCTGTG CATGGGGTGT ACTATGACCC CTCCAAGGAC CTGATTGCTG AGATCCAGAA
 GCAGGGCCAG GGCCAGTGGG CCTACCAAAT CTACCAGGAG CCCTTCAAGA ACCTGAAGAC
 TGGCAAGTAT GCCAGGATGA GGGGGGCCA CACCAATGAT GTGAAGCAGC TGACTGAGGC
 TGTGCAGAAG ATCACCCTG AGTCCATGT GATCTGGGGC AAGACCCCCA AGTTCAAGCT
 10 GCCCATCCAG AAGGAGACCT GGGAGACCTG GTGGACTGAG TACTGGCAGG CCACCTGGAT
 CCCTGAGTGG GAGTTTGTGA ACACCCCCC CCTGGTGAAG CTGTGGTACC AGCTGGAGAA
 GGAGCCCAT TGTGGGGCTG AGACCTTCTA TGTGGATGGG GCTGCCAACA GGGAGACCAA
 GCTGGGCAAG GCTGGCTATG TGACCAACAG GGGCAGGCAG AAGGTGGTGA CCCTGACTGA
 CACCACCAAC CAGAAGACTG AGCTCCAGGC CATCTACCTG GCCCTCCAGG ACTCTGGCCT
 15 GGAGGTGAAC ATTGTGACTG ACTCCAGTA TGCCCTGGGC ATCATCCAGG CCCAGCCTGA
 TCAGTCTGAG TCTGAGCTGG TGAACCAGAT CATTGAGCAG CTGATCAAGA AGGAGAAGGT
 GTACCTGGCC TGGGTGCCTG CCCACAAGGG CATTGGGGGC AATGAGCAGG TGGACAAGCT
 GGTGCTGCT GGCATCAGGA AGGTGCTGTT CCTGGATGGC ATTGACAAGG CCCAGGATGA
 GCATGAGAAG TACCACTCCA ACTGGAGGGC TATGGCCTCT GACTTCAACC TGCCCCCTGT
 20 GGTGGCTAAG GAGATTGTGG CCTCCTGTGA CAAGTGCCAG CTGAAGGGGG AGGCCATGCA
 TGGGCAGGTG GACTGTCTCC CTGGCATCTG GCAGCTGGAC TGCACCCACC TGGAGGGCAA
 GGTGATCCTG GTGGCTGTGC ATGTGGCCTC CGGCTACATT GAGGCTGAGG TGATCCCTGC
 TGAGACAGGC CAGGAGACTG CCTACTTCCT GCTGAAGCTG GCTGGCAGGT GGCCTGTGAA
 GACCATCCAC ACTGACAATG GCTCCAACCT CACTGGGGCC ACAGTGAGGG CTGCCTGCTG
 25 GTGGGCTGGC ATCAAGCAGG AGTTTGGCAT CCCCTACAAC CCCAGTCCC AGGGGGTGGT
 GGAGTCCATG AACAAGGAGC TGAAGAAGAT CATTGGGCAG GTGAGGGACC AGGCTGAGCA
 CCTGAAGACA GCTGTGCAGA TGGCTGTGTT CATCCACAAC TTCAAGAGGA AGGGGGGCAT
 CGGGGGCTAC TCCGCTGGGG AGAGGATTGT GGACATCATT GCCACAGACA TCCAGACCAA
 GGAGCTCCAG AAGCAGATCA CCAAGATCCA GAACTTCAGG GTGTACTACA GGGACTCCAG
 30 GAACCCCTG TGAAGGGCC CTGCCAAGCT GCTGTGGAAG GGGGAGGGGG CTGTGGTGAT
 CCAGGACAAC TCTGACATCA AGGTGGTGCC CAGGAGGAAG GCCAAGATCA TCAGGGACTA
 TGGCAAGCAG ATGGCTGGGG ATGACTGTGT GGCCTCCAGG CAGGATGAGG ACTAAAGCCC
 GGGCAGATCT (SEQ ID NO:5).

The open reading frame of the wild type tPA-pol construct disclosed as SEQ
 35 ID NO:5 contains 875 amino acids, disclosed herein as SEQ ID NO:6, as follows:
 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly

Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ala Pro Ile Ser Pro Ile
Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys Val
Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile
Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu
5 Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr
Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln
Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His Pro Ala Gly Leu Lys
Lys Lys Lys Ser Val Thr Val Leu Asp Val Gly Asp Ala Tyr Phe Ser
Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr Ala Phe Thr Ile Pro
10 Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr Asn Val Leu
Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met Thr
Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr
Gln Tyr Met Asp Asp Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln
His Arg Thr Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly
15 Leu Thr Thr Pro Asp Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp
Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Gln Pro Ile Val
Leu Pro Glu Lys Asp Ser Trp Thr Val Asn Asp Ile Gln Lys Leu Val
Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro Gly Ile Lys Val Arg
Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu Val Ile
20 Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu Ile
Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu
Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile
Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met
Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln
25 Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro Lys Phe
Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr Glu Tyr
Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr Pro Pro
Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val Gly Ala
Glu Thr Phe Tyr Val Asp Gly Ala Ala Asn Arg Glu Thr Lys Leu Gly
30 Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu
Thr Asp Thr Thr Asn Gln Lys Thr Glu Leu Gln Ala Ile Tyr Leu Ala
Leu Gln Asp Ser Gly Leu Glu Val Asn Ile Val Thr Asp Ser Gln Tyr
Ala Leu Gly Ile Ile Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu
Val Asn Gln Ile Ile Glu Gln Leu Ile Lys Lys Glu Lys Val Tyr Leu
35 Ala Trp Val Pro Ala His Lys Gly Ile Gly Gly Asn Glu Gln Val Asp
Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu Phe Leu Asp Gly Ile

Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn Trp Arg Ala
 Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile Val
 Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln
 Val Asp Cys Ser Pro Gly Ile Trp Gln Leu Asp Cys Thr His Leu Glu
 5 Gly Lys Val Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu
 Ala Glu Val Ile Pro Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu
 Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Thr Ile His Thr Asp Asn
 Gly Ser Asn Phe Thr Gly Ala Thr Val Arg Ala Ala Cys Trp Trp Ala
 Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn Pro Gln Ser Gln Gly
 10 Val Val Glu Ser Met Asn Lys Glu Leu Lys Lys Ile Ile Gly Gln Val
 Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val Phe
 Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly
 Glu Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu
 Gln Lys Gln Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp
 15 Ser Arg Asn Pro Leu Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly
 Glu Gly Ala Val Val Ile Gln Asp Asn Ser Asp Ile Lys Val Val Pro
 Arg Arg Lys Ala Lys Ile Ile Arg Asp Tyr Gly Lys Gln Met Ala Gly
 Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp (SEQ ID NO:6) .

The present invention also relates to a codon optimized HIV-1 Pol mutant
 20 contained within a recombinant adenoviral vector such as IA-Pol (SEQ ID NO:4)
 which comprises a leader peptide at the amino terminal portion of the protein, which
 may effect cellular trafficking and hence, immunogenicity of the expressed protein
 within the host cell. Any such adenoviral-based HIV-1 DNA pol mutant disclosed in
 the above paragraphs is suitable for fusion downstream of a leader peptide, such as a
 25 leader peptide including but not limited to the human tPA leader sequence. Therefore,
 any such leader peptide-based HIV-1 pol mutant construct may include but is not
 limited to a mutated DNA molecule which effectively alters the catalytic activity of
 the RT, RNase and/or IN region of the expressed protein, resulting in at least
 substantially decreased enzymatic activity one or more of the RT, RNase H and/or IN
 30 functions of HIV-1 Pol. In a preferred embodiment of this portion of the invention, a
 leader peptide/HIV-1 DNA pol construct contains a mutation or mutations within the
 Pol coding region which effectively abolishes RT, RNase H and IN activity. An
 especially preferable HIV-1 DNA pol construct is a DNA molecule which contains at
 least one point mutation which alters the active site and catalytic activity within the
 35 RT, RNase H and IN domains of Pol, such that each activity is at least substantially
 abolished, and preferably totally abolished. Such a HIV-1 Pol mutant will most likely

comprise at least one point mutation in or around each catalytic domain responsible for RT, RNase H and IN activity, respectfully. An especially preferred embodiment of this portion of the invention relates to a human tPA leader fused to the IA-Pol protein comprising the nine mutations shown in Table 1. The DNA molecule is disclosed
 5 herein as SEQ ID NO:7 and the expressed tPA-IA Pol protein comprises a fusion junction as shown in Figure 18. The complete amino acid sequence of the expressed protein is set forth in SEQ ID NO:8. To this end, SEQ ID NO:7 discloses the nucleotide sequence which codes for a human tPA leader fused to the IA Pol protein comprising the nine mutations shown in Table 1 (herein, "tPA-opt-IApol"). The open
 10 reading frame begins with the initiating Met (nucleotides 8-10) and terminates with a "TAA" codon at nucleotides 2633-2635. The nucleotide sequence encoding tPA-IAPol is also disclosed as follows:

GATCACCATG GATGCAATGA AGAGAGGGCT CTGCTGTGTG CTGCTGCTGT GTGGAGCAGT
 CTTCTGTTTCG CCCAGCGAGA TCTCCGCCCC CATCTCCCCC ATTGAGACTG TGCCTGTGAA
 15 GCTGAAGCCT GGCATGGATG GCCCCAAGGT GAAGCAGTGG CCCCTGACTG AGGAGAAGAT
 CAAGGCCCTG GTGGAAATCT GCACTGAGAT GGAGAAGGAG GGCAAAATCT CCAAGATTGG
 CCCCAGAGAAC CCCTACAACA CCCCTGTGTT TGCCATCAAG AAGAAGGACT CCACCAAGTG
 GAGGAAGCTG GTGGACTTCA GGGAGCTGAA CAAGAGGACC CAGGACTTCT GGGAGGTGCA
 GCTGGGCATC CCCCACCCCG CTGGCCTGAA GAAGAAGAAG TCTGTGACTG TGCTGGCTGT
 20 GGGGGATGCC TACTTCTCTG TGCCCTGGA TGAGGACTTC AGGAAGTACA CTGCCTTCAC
 CATCCCCTCC ATCAACAATG AGACCCCTGG CATCAGGTAC CAGTACAATG TGCTGCCCCA
 GGGCTGGAAG GGCTCCCTCG CCATCTTCCA GTCCTCCATG ACCAAGATCC TGGAGCCCTT
 CAGGAAGCAG AACCTTGACA TTGTGATCTA CCAGTACATG GCTGCCCTGT ATGTGGGCTC
 TGACCTGGAG ATTGGGCAGC ACAGGACCAA GATTGAGGAG CTGAGGCAGC ACCTGCTGAG
 25 GTGGGGCCTG ACCACCCCTG ACAAGAAGCA CCAGAAGGAG CCCCCCTTCC TGTGGATGGG
 CTATGAGCTG CACCCCGACA AGTGGACTGT GCAGCCCATG GTGCTGCCCTG AGAAGGACTC
 CTGGACTGTG AATGACATCC AGAAGCTGGT GGGCAAGCTG AACTGGGCCT CCCAAATCTA
 CCCTGGCATC AAGGTGAGGC AGCTGTGCAA GCTGCTGAGG GGCACCAAGG CCCTGACTGA
 GGTGATCCCC CTGACTGAGG AGGCTGAGCT GGAGCTGGCT GAGAACAGGG AGATCCTGAA
 30 GGAGCCTGTG CATGGGGTGT ACTATGACCC CTCCAAGGAC CTGATTGCTG AGATCCAGAA
 GCAGGGCCAG GGCCAGTGGA CCTACCAAAT CTACCAGGAG CCCTTCAAGA ACCTGAAGAC
 TGGCAAGTAT GCCAGGATGA GGGGGGCCCA CACCAATGAT GTGAAGCAGC TGACTGAGGC
 TGTGCAGAAG ATCACCCTG AGTCCATTGT GATCTGGGGC AAGACCCCA AGTTCAAGCT
 GCCCATCCAG AAGGAGACCT GGGAGACCTG GTGGACTGAG TACTGGCAGG CCACCTGGAT
 35 CCCTGAGTGG GAGTTTGTGA ACACCCCCC CCTGGTGAAG CTGTGGTACC AGCTGGAGAA
 GGAGCCCATG GTGGGGGCTG AGACCTTCTA TGTGGCTGGG GCTGCCAACA GGGAGACCAA

GCTGGGCAAG GCTGGCTATG TGACCAACAG GGGCAGGCAG AAGGTGGTGA CCCTGACTGA
 CACCACCAAC CAGAAGACTG CCCTCCAGGC CATCTACCTG GCCCTCCAGG ACTCTGGCCT
 GGAGGTGAAC ATTGTGACTG CCTCCCAGTA TGCCCTGGGC ATCATCCAGG CCCAGCCTGA
 TCAGTCTGAG TCTGAGCTGG TGAACCAGAT CATTGAGCAG CTGATCAAGA AGGAGAAGGT
 5 GTACCTGGCC TGGGTGCCCTG CCCACAAGGG CATTGGGGGC AATGAGCAGG TGGACAAGCT
 GGTGTCTGCT GGCATCAGGA AGGTGCTGTT CCTGGATGGC ATTGACAAGG CCCAGGATGA
 GCATGAGAAG TACCACTCCA ACTGGAGGGC TATGGCCTCT GACTTCAACC TGCCCCCTGT
 GGTGGCTAAG GAGATTGTGG CCTCCTGTGA CAAGTGCCAG CTGAAGGGGG AGGCCATGCA
 TGGGCAGGTG GACTGCTCCC CTGGCATCTG GCAGCTGGCC TGCACCCACC TGGAGGGCAA
 10 GGTGATCCTG GTGGCTGTGC ATGTGGCCTC CGGCTACATT GAGGCTGAGG TGATCCCTGC
 TGAGACAGGC CAGGAGACTG CCTACTTCCT GCTGAAGCTG GCTGGCAGGT GGCCTGTGAA
 GACCATCCAC ACTGCCAATG GCTCCAATT CACTGGGGCC ACAGTGAGGG CTGCCTGCTG
 GTGGGCTGGC ATCAAGCAGG AGTTTGGCAT CCCCTACAAC CCCCAGTCCC AGGGGGTGGT
 GGCCTCCATG AACAAGGAGC TGAAGAAGAT CATTGGGCAG GTGAGGGACC AGGCTGAGCA
 15 CCTGAAGACA GCTGTGCAGA TGGCTGTGTT CATCCACAAC TTCAAGAGGA AGGGGGGCAT
 CGGGGGCTAC TCCGCTGGGG AGAGGATTGT GGACATCATT GCCACAGACA TCCAGACCAA
 GGAGCTCCAG AAGCAGATCA CCAAGATCCA GAACTTCAGG GTGTACTACA GGGACTCCAG
 ACCCCCTG TGGAAGGGCC CTGCCAAGCT GCTGTGGAAG GGGGAGGGGG CTGTGGTGAT
 CCAGGACAAC TCTGACATCA AGGTGGTGCC CAGGAGGAAG GCCAAGATCA TCAGGGACTA
 20 TGGCAAGCAG ATGGCTGGGG ATGACTGTGT GGCCTCCAGG CAGGATGAGG ACTAAAGCCC
 GGGCAGATCT (SEQ ID NO:7).

The open reading frame of the tPA-IA-pol construct disclosed as SEQ ID NO:7 contains 875 amino acids, disclosed herein as tPA-IA-Pol and SEQ ID NO:8, as follows:

25 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ala Pro Ile Ser Pro Ile
 Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys Val
 Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile
 Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu
 30 Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr
 Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln
 Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His Pro Ala Gly Leu Lys
 Lys Lys Lys Ser Val Thr Val Leu Ala Val Gly Asp Ala Tyr Phe Ser
 Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr Ala Phe Thr Ile Pro
 35 Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr Asn Val Leu
 Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met Thr

Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr
Gln Tyr Met Ala Ala Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln
His Arg Thr Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly
Leu Thr Thr Pro Asp Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp
5 Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Gln Pro Ile Val
Leu Pro Glu Lys Asp Ser Trp Thr Val Asn Asp Ile Gln Lys Leu Val
Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro Gly Ile Lys Val Arg
Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu Val Ile
Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu Ile
10 Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu
Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile
Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met
Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln
Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro Lys Phe
15 Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr Glu Tyr
Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr Pro Pro
Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val Gly Ala
Glu Thr Phe Tyr Val Ala Gly Ala Ala Asn Arg Glu Thr Lys Leu Gly
Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu
20 Thr Asp Thr Thr Asn Gln Lys Thr Ala Leu Gln Ala Ile Tyr Leu Ala
Leu Gln Asp Ser Gly Leu Glu Val Asn Ile Val Thr Ala Ser Gln Tyr
Ala Leu Gly Ile Ile Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu
Val Asn Gln Ile Ile Glu Gln Leu Ile Lys Lys Glu Lys Val Tyr Leu
Ala Trp Val Pro Ala His Lys Gly Ile Gly Gly Asn Glu Gln Val Asp
25 Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu Phe Leu Asp Gly Ile
Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn Trp Arg Ala
Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile Val
Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln
Val Asp Cys Ser Pro Gly Ile Trp Gln Leu Ala Cys Thr His Leu Glu
30 Gly Lys Val Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu
Ala Glu Val Ile Pro Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu
Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Thr Ile His Thr Ala Asn
Gly Ser Asn Phe Thr Gly Ala Thr Val Arg Ala Ala Cys Trp Trp Ala
Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn Pro Gln Ser Gln Gly
35 Val Val Ala Ser Met Asn Lys Glu Leu Lys Lys Ile Ile Gly Gln Val
Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val Phe

Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly
 Glu Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu
 Gln Lys Gln Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp
 Ser Arg Asn Pro Leu Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly
 5 Glu Gly Ala Val Val Ile Gln Asp Asn Ser Asp Ile Lys Val Val Pro
 Arg Arg Lys Ala Lys Ile Ile Arg Asp Tyr Gly Lys Gln Met Ala Gly
 Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp (SEQ ID NO:8) .

EXAMPLE 18

10 CODON OPTIMIZED HIV-1 NEF AND CODON OPTIMIZED HIV-1 NEF MODIFICATIONS

Codon optimized version of HIV-1 Nef and HIV-1 Nef modifications are essentially as described in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed
 15 December 15, 2000, both documents which are hereby incorporated by reference. As disclosed within the above-mentioned documents, particular embodiments of codon optimized Nef and Nef modifications relate to a DNA molecule encoding HIV-1 Nef from the HIV-1 jf1 isolate wherein the codons are optimized for expression in a mammalian system such as a human. The DNA molecule which encodes this protein
 20 is disclosed herein as SEQ ID NO:9, while the expressed open reading frame is disclosed herein as SEQ ID NO:10. Another embodiment of Nef-based coding regions for use in the adenoviral vectors of the present invention comprise a codon optimized DNA molecule encoding a protein containing the human plasminogen activator (tpa) leader peptide fused with the NH₂-terminus of the HIV-1 Nef
 25 polypeptide. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:11, while the expressed open reading frame is disclosed herein as SEQ ID NO:12. Another modified Nef optimized coding region relates to a DNA molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and
 30 substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175, herein described as opt nef (G2A, LLAA). The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:13, while the expressed open reading frame is disclosed herein as SEQ ID NO:14. An additional embodiment relates to a DNA molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation
 35 site and dileucine motif have been deleted, as well as comprising a tPA leader peptide. This DNA molecule, opt tpanef (LLAA), comprises an open reading frame which

encodes a Nef protein containing a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef (jfr1), wherein Leu-174 and Leu-175 are substituted with Ala-174 and Ala-175, herein referred to as opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, while the expressed open reading frame is disclosed herein as SEQ ID NO:16.

5 As disclosed in the above-identified documents (U.S. Application Serial No. 09/738,782 and PCT International Application PCT/US00/34162) and reiterated herein, the following nef-based nucleotide and amino acid sequences which comprise the respective open reading frame are as follows:

1. The nucleotide sequence of the codon optimized version of HIV-1 jfr1 nef gene is disclosed herein as SEQ ID NO:9, as shown herein:

10 GATCTGCCAC CATGGGCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA
GGGAGAGGAT GAGGAGGGCC GAGCCCGCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG
CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCCTCCA
ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG
15 GCTTCCCCGT GAGGCCCCAG GTGCCCTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC
TGTCCTCACTT CCTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC
AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT
AATACCCCGG CCCCGGCATC AGGTTCCTCC TGACCTTCGG CTGGTGCTTC AAGCTGGTGC
CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAACTGC CTGCTGCACC
20 CCATGTCCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTGACT
CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT
AAAGCCCGGG C (SEQ ID NO:9).

Preferred codon usage is as follows: Met (ATG), Gly (GGC), Lys (AAG),
Trp (TGG), Ser (TCC), Arg (AGG), Val (GTG), Pro (CCC), Thr (ACC), Glu (GAG);
25 Leu (CTG), His (CAC), Ile (ATC), Asn (AAC), Cys (TGC), Ala (GCC), Gln (CAG),
Phe (TTC) and Tyr (TAC). For an additional discussion relating to mammalian
(human) codon optimization, see WO 97/31115 (PCT/US97/02294), which is hereby
incorporated by reference. See also Figure 19A-B for a comparison of wild type vs.
codon optimized nucleotides comprising the open reading frame of HIV-Nef.

30 The open reading frame for SEQ ID NO:9 above comprises an initiating
methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides
660-662. The open reading frame of SEQ ID NO:9 provides for a 216 amino acid
HIV-1 Nef protein expressed through utilization of a codon optimized DNA vaccine
vector. The 216 amino acid HIV-1 Nef (jfr1) protein is disclosed herein as SEQ ID
35 NO:10, and as follows:

Met Gly Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val

Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg
 Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu
 Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp
 Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val
 5 Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp
 Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His
 Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln
 Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg
 Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro
 10 Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Leu Leu His
 Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu
 Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu
 His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:10).

HIV-1 Nef is a 216 amino acid cytosolic protein which associates with the
 15 inner surface of the host cell plasma membrane through myristylation of Gly-2
 (Franchini et al., 1986, *Virology* 155: 593-599). While not all possible Nef functions
 have been elucidated, it has become clear that correct trafficking of Nef to the inner
 plasma membrane promotes viral replication by altering the host intracellular
 environment to facilitate the early phase of the HIV-1 life cycle and by increasing the
 20 infectivity of progeny viral particles. In one aspect of the invention regarding
 codon-optimized, protein-modified polypeptides, the nef-encoding region of the
 adenovirus vector of the present invention is modified to contain a nucleotide
 sequence which encodes a heterologous leader peptide such that the amino terminal
 region of the expressed protein will contain the leader peptide. The diversity of
 25 function that typifies eukaryotic cells depends upon the structural differentiation of
 their membrane boundaries. To generate and maintain these structures, proteins must
 be transported from their site of synthesis in the endoplasmic reticulum to
 predetermined destinations throughout the cell. This requires that the trafficking
 proteins display sorting signals that are recognized by the molecular machinery
 30 responsible for route selection located at the access points to the main trafficking
 pathways. Sorting decisions for most proteins need to be made only once as they
 traverse their biosynthetic pathways since their final destination, the cellular location
 at which they perform their function, becomes their permanent residence.
 Maintenance of intracellular integrity depends in part on the selective sorting and
 35 accurate transport of proteins to their correct destinations. Defined sequence motifs
 exist in proteins which can act as 'address labels'. A number of sorting signals have

been found associated with the cytoplasmic domains of membrane proteins. An effective induction of CTL responses often required sustained, high level endogenous expression of an antigen. As membrane-association via myristylation is an essential requirement for most of Nef's function, mutants lacking myristylation, by glycine-to-alanine change, change of the dileucine motif and/or by substitution with a tpa leader sequence as described herein, will be functionally defective, and therefore will have improved safety profile compared to wild-type Nef for use as an HIV-1 vaccine component.

In another embodiment of this portion of the invention, either the DNA vector or the HIV-1 nef nucleotide sequence is modified to include the human tissue-specific plasminogen activator (tPA) leader. As shown in Figure 16A-B, a DNA vector may be modified by known recombinant DNA methodology to contain a leader signal peptide of interest, such that downstream cloning of the modified HIV-1 protein of interest results in a nucleotide sequence which encodes a modified HIV-1 tPA/Nef protein. In the alternative, as noted above, insertion of a nucleotide sequence which encodes a leader peptide may be inserted into a DNA vector housing the open reading frame for the Nef protein of interest. Regardless of the cloning strategy, the end result is a polynucleotide vaccine which comprises vector components for effective gene expression in conjunction with nucleotide sequences which encode a modified HIV-1 Nef protein of interest, including but not limited to a HIV-1 Nef protein which contains a leader peptide. The amino acid sequence of the human tPA leader utilized herein is as follows: MDAMKRGGLCCVLLLCGAVFVSPSEISS (SEQ ID NO:17).

It has been shown that myristylation of Gly-2 in conjunction with a dileucine motif in the carboxy region of the protein is essential for Nef-induced down regulation of CD4 (Aiken et al., 1994, *Cell* 76: 853-864) via endocytosis. It has also been shown that Nef expression promotes down regulation of MHCI (Schwartz et al., 1996, *Nature Medicine* 2(3): 338-342) via endocytosis. The present invention relates in part to DNA vaccines which encode modified Nef proteins altered in trafficking and/or functional properties. The modifications introduced into the adenoviral vector HIV vaccines of the present invention include but are not limited to additions, deletions or substitutions to the nef open reading frame which results in the expression of a modified Nef protein which includes an amino terminal leader peptide, modification or deletion of the amino terminal myristylation site, and modification or deletion of the dileucine motif within the Nef protein and which alter function within the infected host cell. Therefore, a central theme of the DNA molecules and recombinant adenoviral HIV vaccines of the present invention is (1)

host administration and intracellular delivery of a codon optimized nef-based
 adenoviral HIV vaccine; (2) expression of a modified Nef protein which is
 immunogenic in terms of eliciting both CTL and Th responses; and, (3) inhibiting or
 at least altering known early viral functions of Nef which have been shown to
 5 promote HIV-1 replication and load within an infected host. Therefore, the nef
 coding region may be altered, resulting in a DNA vaccine which expresses a modified
 Nef protein wherein the amino terminal Gly-2 myristylation residue is either deleted
 or modified to express alternate amino acid residues. Also, the nef coding region may
 be altered so as to result in a DNA vaccine which expresses a modified Nef protein
 10 wherein the dileucine motif is either deleted or modified to express alternate amino
 acid residues. In addition, the adenoviral vector HIV vaccines of the present
 invention also relate to an isolated DNA molecule, regardless of codon usage, which
 expresses a wild type or modified Nef protein as described herein, including but not
 limited to modified Nef proteins which comprise a deletion or substitution of Gly 2, a
 15 deletion or substitution of Leu 174 and Leu 175 and/or inclusion of a leader sequence.

Therefore, specific Nef-based constructs further include the following, as
 exemplification's and not limitations. For example, the present invention relates to an
 adenoviral vector vaccine which encodes modified forms of HIV-1, an open reading
 frame which encodes a Nef protein which comprises a tPA leader sequence fused to
 20 amino acid residue 6-216 of HIV-1 Nef (jfr1) is referred to herein as opt tpanef. The
 nucleotide sequence comprising the open reading frame of opt tpanef is disclosed
 herein as SEQ ID NO:11, as shown below:

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CATGGATGCA ATGAAGAGAG GGCTCTGCTG TGTGCTGCTG CTGTGTGGAG CAGTCTTCGT
TTCGCCCAGC GAGATCTCCT CCAAGAGGTC CGTGCCCGGC TGGTCCACCG TGAGGGAGAG
25 GATGAGGAGG GCCGAGCCCG CCGCCGACAG GGTGAGGAGG ACCGAGCCCG CCGCCGTGGG
CGTGGGCGCC GTGTCCAGGG ACCTGGAGAA GCACGGCGCC ATCACCTCCT CCAACACCGC
CGCCACCAAC GCCGACTGCG CCTGGCTGGA GGCCAGGAG GACGAGGAGG TGGGCTTCCC
CGTGAGGCCC CAGGTGCCCC TGAGGCCCAT GACCTACAAG GGCGCCGTGG ACCTGTCCCA
CTTCCTGAAG GAGAAGGGCG GCCTGGAGGG CCTGATCCAC TCCCAGAAGA GGCAGGACAT
30 CCTGGACCTG TGGGTGTACC ACACCCAGGG CTACTTCCCC GACTGGCAGA ACTACACCCC
CGGCCCCGGC ATCAGGTTCC CCCTGACCTT CGGCTGGTGC TTCAAGCTGG TGCCCGTGGA
GCCCCAGAAG GTGGAGGAGG CCAACGAGGG CGAGAACAAAC TGCCTGCTGC ACCCATGTC
CCAGCACGGC ATCAGGAGC CCGAGAAGGA GGTGCTGGAG TGGAGGTTCT ACTCCAAGCT
GGCCTTCCAC CACGTGGCCA GGGAGCTGCA CCCCAGGTAC TACAAGGACT GCTAAAGCC
35 (SEQ ID NO:11) .

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The open reading frame for SEQ ID NO:11 comprises an initiating methionine

residue at nucleotides 2-4 and a "TAA" stop codon from nucleotides 713-715. The open reading frame of SEQ ID NO:3 provides for a 237 amino acid HIV-1 Nef protein which comprises a tPA leader sequence fused to amino acids 6-216 of HIV-1 Nef, including the dileucine motif at amino acid residues 174 and 175. This 237 amino acid tPA/Nef (jfr1) fusion protein is disclosed herein as SEQ ID NO:12, and is shown as follows:

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ser Lys Arg Ser Val Pro
 Gly Trp Ser Thr Val Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala
 10 Asp Arg Val Arg Arg Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val
 Ser Arg Asp Leu Glu Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala
 Ala Thr Asn Ala Asp Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu
 Val Gly Phe Pro Val Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr
 Lys Gly Ala Val Asp Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu
 15 Glu Gly Leu Ile His Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp
 Val Tyr His Thr Gln Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro
 Gly Pro Gly Ile Arg Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu
 Val Pro Val Glu Pro Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn
 Asn Cys Leu Leu His Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu
 20 Lys Glu Val Leu Glu Trp Arg Phe Asp Ser Lys Leu Ala Phe His His
 Val Ala Arg Glu Leu His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:12).

Therefore, this exemplified Nef protein, Opt tPA-Nef, contains both a tPA leader sequence as well as deleting the myristylation site of Gly-2A DNA molecule encoding HIV-1 Nef from the HIV-1 jfr1 isolate wherein the codons are optimized for expression in a mammalian system such as a human.

In another specific embodiment of the present invention, a DNA molecule is disclosed which encodes optimized HIV-1 Nef wherein the open reading frame of a recombinant adenoviral HIV vaccine encodes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175. This open reading frame is herein described as opt nef (G2A,LLAA) and is disclosed as SEQ ID NO:13, which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662. The nucleotide sequence of this codon optimized version of HIV-1 jfr1 nef gene with the above mentioned modifications is disclosed herein as SEQ ID NO:13, as follows:

GATCTGCCAC CATGGCCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA
 GGGAGAGGAT GAGGAGGGCC GAGCCCGCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG
 CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCCTCCA
 ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG
 5 GCTTCCCCGT GAGGCCCCAG GTGCCCCCTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC
 TGTCCCACTT CCTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC
 AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT
 ACACCCCCGG CCCCAGCATC AGGTTCCCCC TGACCTTCGG CTGGTGCTTC AAGCTGGTGC
 CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAACTGC GCCGCCACC
 10 CCATGTCCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTCGACT
 CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT
 AAAGCCCGGG C (SEQ ID NO:13).

The open reading frame of SEQ ID NO:13 encodes Nef (G2A,LLAA), disclosed herein as SEQ ID NO:14, as follows:

15 Met Ala Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val
 Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg
 Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu
 Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp
 Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val
 20 Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp
 Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His
 Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln
 Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg
 Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro
 25 Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Ala Ala His
 Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu
 Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu
 His Pro Glu Tyr Tyr Lys Asp Cys Ser (SEQ ID NO:14).

An additional embodiment of the present invention relates to another DNA
 30 molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation
 site and dileucine motif have been deleted, as well as comprising a tPA leader peptide.
 This DNA molecule, opt tpanef (LLAA) comprises an open reading frame which
 encodes a Nef protein containing a tPA leader sequence fused to amino acid residue
 6-216 of HIV-1 Nef (jfrl), wherein Leu-174 and Leu-175 are substituted with Ala-174
 35 and Ala-175 (Ala-195 and Ala-196 in this tPA-based fusion protein). The nucleotide

sequence comprising the open reading frame of opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, as shown below:

5 CATGGATGCA ATGAAGAGAG GGCTCTGCTG TGTGCTGCTG CTGTGTGGAG CAGTCTTCGT
TTCGCCCAGC GAGATCTCCT CCAAGAGGTC CGTGCCCGGC TGGTCCACCG TGAGGGAGAG
GATGAGGAGG GCCGAGCCCG CCGCCGACAG GGTGAGGAGG ACCGAGCCCG CCGCCGTGGG
10 CGTGGGCGCC GTGTCCAGGG ACCTGGAGAA GCACGGCGCC ATCACCTCCT CCAACACCGC
CGCCACCAAC GCCGACTGCG CCTGGCTGGA GGCCAGGAG GACGAGGAGG TGGGCTTCCC
CGTGAGGCCC CAGGTGCCCC TGAGGCCCCAT GACCTACAAG GGCGCCGTGG ACCTGTCCCA
CTTCCTGAAG GAGAAGGGCG GCCTGGAGGG CCTGATCCAC TCCCAGAAGA GGCAGGACAT
15 CCTGGACCTG TGGGTGTACC ACACCCAGGG CTACTTCCCC GACTGGCAGA ACTACACCCC
CGGCCCCGGC ATCAGGTTCC CCCTGACCTT CGGCTGGTGC TTCAAGCTGG TGCCCGTGGG
GCCCCAGAAG GTGGAGGAGG CCAACGAGGG CGAGAACAAC TGCGCCGCCC ACCCATGTG
CCAGCACGGC ATCGAGGACC CCGAGAAGGA GGTGCTGGAG TGGAGGTTTCG ACTCCAAGCT
GGCCTTCCAC CACGTGGCCA GGGAGCTGCA CCCCAGTAC TACAAGGACT GCTAAAGCCC
15 (SEQ ID NO:15).

The open reading frame of SEQ ID NO:7 encoding tPA-Nef (LLAA), disclosed herein as SEQ ID NO:16, is as follows:

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly
Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ser Lys Arg Ser Val Pro
20 Gly Trp Ser Thr Val Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala
Asp Arg Val Arg Arg Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val
Ser Arg Asp Leu Glu Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala
Ala Thr Asn Ala Asp Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu
Val Gly Phe Pro Val Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr
25 Lys Gly Ala Val Asp Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu
Glu Gly Leu Ile His Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp
Val Tyr His Thr Gln Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro
Gly Pro Gly Ile Arg Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu
Val Pro Val Glu Pro Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn
30 Asn Cys Ala Ala His Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu
Lys Glu Val Leu Glu Trp Arg Phe Asp Ser Lys Leu Ala Phe His His
Val Ala Arg Glu Leu His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:16).

An adenoviral vector of the present invention may comprise a DNA sequence, regardless of codon usage, which expresses a wild type or modified Nef protein as described herein, including but not limited to modified Nef proteins which comprise a deletion or substitution of Gly 2, a deletion or substitution of Leu 174 and Leu 175

and/or inclusion of a leader sequence. Therefore, partial or fully codon optimized DNA vaccine expression vector constructs are preferred since such constructs should result in increased host expression. However, it is within the scope of the present invention to utilize "non-codon optimized" versions of the constructs disclosed herein, especially modified versions of HIV Nef which are shown to promote a substantial cellular immune response subsequent to host administration.

Figure 20A-C show nucleotide sequences at junctions between nef coding sequence and plasmid backbone of nef expression vectors V1Jns/nef (Figure 20A), V1Jns/nef(G2A,LLAA) (Figure 20B), V1Jns/tpanef (Figure 20C) and V1Jns/tpanef(LLAA) (Figure 20C, also). 5' and 3' flanking sequences of codon optimized nef or codon optimized nef mutant genes are indicated by bold/italic letters; nef and nef mutant coding sequences are indicated by plain letters. Also indicated (as underlined) are the restriction endonuclease sites involved in construction of respective nef expression vectors. V1Jns/tpanef and V1Jns/tpanef(LLAA) have identical sequences at the junctions.

Figure 21 shows a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine 174 and 175 are the sites involved in myristylation and dileucine motif, respectively.

20

EXAMPLE 19

MRKAd5Pol Construction and Virus Rescue

Construction of vector: shuttle plasmid and pre-adenovirus plasmid - Key steps performed in the construction of the vectors, including the pre-adenovirus plasmid denoted MRKAd5pol, is depicted in Figure 22. Briefly, the adenoviral shuttle vector for the full-length inactivated HIV-1 pol gene is as follows. The vector MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) is a derivative of the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. The vector contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*II site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1-/E3+)Cla1 (or MRKpAdHVE3) pre-plasmid. The vector, similar to the original shuttle vector contains the *Pac*I site, extension to the packaging signal region, and extension to the pIX gene. The synthetic full-length codon-optimized HIV-1 pol gene was isolated directly from the plasmid pV1Jns-HIV-pol-inact(opt). Digestion of this plasmid with *Bgl* II releases the pol

gene intact (comprising a codon optimized IA pol sequence as disclosed in SEQ ID NO:3). The pol fragment was gel purified and ligated into the MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) shuttle vector at the *Bgl*III site. The clones were checked for the correct orientation of the gene by using
 5 restriction enzymes *Dra*III/*Not*I. A positive clone was isolated and named MRKpdel+hCMVmin+FL-pol+bGHpA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows. Shuttle plasmid MRKpdel+hCMVmin+FL-pol+bGHpA(S) was digested with restriction enzymes *Pac*I and *Bst*1107 I (or its
 10 isoschizomer, *Bst*Z107 I) and then co-transformed into *E. coli* strain BJ5183 with linearized (*Clal* digested) adenoviral backbone plasmid, MRKpAd(E1-/E3+)*Clal*. The resulting pre-plasmid originally named MRKpAd+hCMVmin+FL-pol+bGHpA(S)E3+ is now referred to as "pMRKAd5pol". The genetic structure of the resulting pMRKAd5pol was verified by PCR, restriction enzyme and DNA
 15 sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the pol transgene in transient transfection cell culture. The complete nucleotide sequence of this pMRKAd5HIV-1pol adenoviral vector is shown in Figure 26 A-AO.

20 *Generation of research-grade recombinant adenovirus* - The pre-adenovirus plasmid, pMRKAd5pol, was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAd5pol was digested with restriction enzyme *Pac*I (New England Biolabs) and 3.3 µg was transfected per 6 cm dish of PER.C6[®] cells using the calcium phosphate co-
 25 precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech Inc.). *Pac*I digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested 6 -10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at ≤ -60°C. This pol containing
 30 recombinant adenovirus is referred to herein as "MRKAd5pol". This recombinant adenovirus expresses an inactivated HIV-1 Pol protein as shown in SEQ ID NO:6.

EXAMPLE 20

MRKAd5Nef Construction and Virus Rescue

35 *Construction of vector: shuttle plasmid and pre-adenovirus plasmid* - Key steps performed in the construction of the vectors, including the pre-adenovirus

plasmid denoted MRKAd5nef, is depicted in Figure 23. Briefly, as shown in Example 19 above, the vector MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHPA(str.) is the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. It has been modified to contain the *Pac1* site, extension to the packaging signal region, and extension to the pIX gene. It contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl11* site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1-/E3+)Cla1 pre-plasmid. The synthetic full-length codon-optimized HIV-1 nef gene was isolated directly from the plasmid pV1Jns/nef (G2A,LLAA). Digestion of this plasmid with *Bgl11* releases the pol gene intact, which comprises the nucleotide sequence as disclosed in SEQ ID NO:13. The nef fragment was gel purified and ligated into the MRKpdeIE1+CMVmin+BGHPA(str.) shuttle vector at the *Bgl11* site. The clones were checked for correction orientation of the gene by using restriction enzyme *Sca1*. A positive clone was isolated and named MRKpdeIE1hCMVminFL-nefBGHPA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows. Shuttle plasmid MRKpdeIE1hCMVminFL-nefBGHPA(s) was digested with restriction enzymes *Pac1* and *Bst1107 I* (or its isoschizomer, *BstZ107 I*) and then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla1* digested) adenoviral backbone plasmid, MRKpAd(E1/E3+)Cla1. The resulting pre-plasmid originally named MRKpdeIE1hCMVminFL-nefBGHPA(s) is now referred to as "pMRKAd5nef". The genetic structure of the resulting pMRKAd5nef was verified by PCR, restriction enzyme and DNA sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the nef transgene in transient transfection cell culture. The complete nucleotide sequence of this pMRKAd5HIV-1nef adenoviral vector is shown in Figure 27A-AM.

Generation of research-grade recombinant adenovirus - The pre-adenovirus plasmid, pMRKAd5nef, was rescued as infectious virions in PER.C6[®] adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAdnef was digested with restriction enzyme *Pac1* (New England Biolabs) and 3.3 µg was transfected per 6 cm dish of PER.C6[®] cells using the calcium phosphate co-precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech

Inc.). *Pac1* digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6[®] cells. Infected cells and media were harvested 6 -10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at $\leq -60^{\circ}\text{C}$. This nef containing recombinant adenovirus is now referred to as "MRKAd5nef".

EXAMPLE 21

Construction of Murine CMV Promoter Containing Shuttle Vectors for Inactivated Pol and Nef/G2A,LLAA

10 The murine CMV (mCMV) was amplified from the plasmid pMH4 (supplied by Frank Graham, McMaster University) using the primer set: mCMV (*Not* I) Forward: 5'-ATA AGA ATG CGG CCG CCA TAT ACT GAG TCA TTA GG-3' (SEQ ID NO: 20); mCMV (*Bgl* II) Reverse: 5'-AAG GAA GAT CTA CCG ACG CTG GTC GCG CCT C-3' (SEQ ID NO:21). The underlined nucleotides represent the *Not* I and the *Bgl* II sites respectively for each primer. This PCR amplicon was used for the construction of the mCMV shuttle vector containing the transgene in the E1 parallel orientation. The hCMV promoter was removed from the original shuttle vector (containing the hCMV-gag-bGHpA transgene in the E1 parallel orientation) by digestion with *Not* I and *Bgl* II. The mCMV promoter (*Not* I/*Bgl* II digested PCR product) was inserted into the shuttle vector in a directional manner. The shuttle vector was then digested with *Bgl* II and the gag reporter gene (*Bgl* II fragment) was re-inserted back into the shuttle vector. Several clones were screened for correct orientation of the reporter gene. For the construction of the mCMV-gag in the E1 antiparallel orientation, the mCMV promoter was amplified from the plasmid pMH4 using the following primer set: mCMV (*Asc* I) Forward: 5'- ATA AGA ATG GCG CGC CAT ATA CTG AGT CAT TAG G (SEQ ID NO:22); mCMV (*Bgl* II) Reverse: 5' AAG GAA GAT CTA CCG ACG CTG GTC GCG CCT C (SEQ ID NO:23). The underlined nucleotides represent the *Asc* I and *Bgl* II sites, respectively for each primer. The shuttle vector containing the hCMV-gag transgene in the E1 antiparallel orientation was digested with *Asc* I and *Bgl* II to remove the hCMV-gag portion of the transgene. The mCMV promoter (*Asc* I/*Bgl* II digested PCR product) was inserted into the shuttle vector in a directional manner. The vector was then digested with *Bgl* II and the gag reporter gene (*Bgl* II fragment) was re-inserted. Several clones were screened for correct orientation of the reporter gene. For each of the full length IA pol and full length nef/G2A,LLAA genes, cloning was performed using the unique

Bgl II site within the mCMV-bGHpA shuttle vector. The pol and nef genes were excised from their respective pV1Jns plasmids by *Bgl* II digestion.

EXAMPLE 22

5 Construction of mCMV Full Length Inactivated Pol and Full Length nef/G2A.LLAA Adenovectors

Each of these transgenes of Example 21 were inserted into the modified shuttle vector in both the E1 parallel and E1 anti-parallel orientations. *Pac*I and *Bst*Z110I digestion of each shuttle vector was performed and each specific transgene
10 fragment containing the flanking Ad5 sequences was isolated and co-transformed with *Cla*I digested MRKpAd5(E3+) or MRKpAd5(E3-) adenovector plasmids via bacterial homologous recombination in BJ5183 *E. coli* cells. Recombinant pre-plasmid adenovectors containing the various transgenes in both the E3- and E3+ versions (and in the E1 parallel and E1 antiparallel orientations) were subsequently
15 prepared in large scale following transformation into XL-1 Blue *E. coli* cells and analyzed by restriction analysis and sequencing.

EXAMPLE 23

Construction of hCMV-tpa-nef (LLAA) Adenovector

20 The tpa-nef gene was amplified out from GMP grade pV1Jns-tpanef (LLAA) vector using the primer sets: Tpanef (*Bam*HI) F 5'-ATT GGA TCC ATG GAT GCA ATG AAG AGA GGG (SEQ ID 24); Tpanef (*Bam*HI) R 5'-ATA GGA TCC TTA GCA GTC CTT GTA GTA CTC G (SEQ ID NO:25). The resulting PCR product was digested with *Bam*HI, gel purified and cloned into the *Bgl* II site of MRKAd5CMV-bGHpA shuttle vector (*Bgl* II digested and calf intestinal phosphatase treated).
25 Clones containing the tpanef (LLAA) gene (see SEQ ID NO:15 for complet coding region) in the correct orientation with respect to the hCMV promoter were selected following *Sca*I digestion. The resulting MRKAd5tpanef shuttle vector was digested with *Pac*I and *Bst*Z110I and cloned into the E3+ MRKAd5 adenovector via bacterial
30 homologous recombination techniques.

EXAMPLE 24

Immunogenicity of MRKAd5pol and MRKAd5nef Vaccine

Materials and Methods - Rodent Immunization - Groups of N=10 BALB/c
35 mice were immunized i.m. with the following vectors: (1) MRKAd5hCMV-IApol (E3+) at either 10^7 vp and 10^9 vp; and (2) MRKAd5hCMV-IApol (E3-) at either

10⁷ vp and 10⁹ vp. At 7 weeks post dose, 5 of the 10 mice per cohort were boosted with the same vector and dose they initially received. At 3 weeks post the second does, sera and spleens were collected from all the animals for RT ELISA and IFNg ELISpot analyses, respectively. For all rodent immunizations, the Ad5 vectors were
5 diluted in 5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM MgCl₂, 0.005% polysorbate 80, pH 8.0. The total dose was injected to both quadricep muscles in 50 µL aliquots using a 0.3-mL insulin syringe with 28-1/2G needles (Becton-Dickinson, Franklin Lakes, NJ).

Groups of N=10 C57/BL6 mice were immunized i.m. with the following
10 vectors: (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+) at either 10⁷ vp and 10⁹ vp; (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10⁷ vp and 10⁹ vp; and (3) MRKAd5mCMV-tpanef(LLAA) (E3+) at either 10⁷ vp and 10⁹ vp. At 7 weeks post dose, 5 of the 10 mice per cohort were boosted with the same vector and dose they initially received. At 3 weeks post the second does, sera and spleens were
15 collected from all the animals for RT ELISA and IFNg ELISpot analyses, respectively.

Non-human Primate immunization - Cohorts of 3 rhesus macaques (2-3 kg) were vaccinated with the following Ad vectors: (1) MRKAd5hCMV-IAPol (E3+) at either 10⁹ vp and 10¹¹ vp dose; and (2) MRKAd5hCMV-IAPol (E3-) at either
20 10⁹ vp and 10¹¹ vp; (3) MRKAd5hCMV-nef(G2A,LLAA) (E3+) at either 10⁹ vp and 10¹¹ vp; and (4) MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10⁹ vp and 10¹¹ vp. The vaccine was administered to chemically restrained monkeys (10 mg/kg ketamine) by needle injection of two 0.5 mL aliquots of the Ad vectors (in 5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM MgCl₂, 0.005% polysorbate 80, pH 8.0)
25 into both deltoid muscles. The animals were immunized twice at a 4 week interval (T=0, 4 weeks).

Murine anti-RT and anti-nef ELISA - Anti-RT titers were obtained following standard secondary antibody-based ELISA. Maxisorp plates (NUNC, Rochester, NY) were coated by overnight incubation with 100 µL of 1 µg/mL HIV-1 RT protein
30 (Advanced Biotechnologies, Columbia, MD) in PBS. For anti-nef ELISA, 100 µL of 1 µg/mL HIV-1 nef (Advanced Biotechnologies, Columbia, MD) was used to coat the plates. The plates were washed with PBS/0.05% Tween 20 using Titertek MAP instrument (Huntsville, AL) and incubated for 2 h with 200 µL/well of blocking solution (PBS/0.05% tween/1% BSA). An initial serum dilution of 100-fold was
35 performed followed by 4-fold serial dilution. 100-µL aliquots of serially diluted samples were added per well and incubated for 2 h at room temperature. The plates

were washed and 100 μ L of 1/1000-diluted HRP-rabbit anti-mouse IgG (ZYMED, San Francisco, CA) were added with 1 h incubation. The plates were washed thoroughly and soaked with 100 μ L 1,2-phenylenediamine dihydrochloride/hydrogen peroxide (DAKO, Norway) solution for 15 min. The reaction was quenched by
 5 adding 100 μ L of 0.5M H₂SO₄ per well. OD₄₉₂ readings were recorded using Titertek Multiskan MCC/340 with S20 stacker. Endpoint titers were defined as the highest serum dilution that resulted in an absorbance value of greater than or equal to 0.1 OD₄₉₂ (2.5 times the background value).

Non-human primate and murine ELISpot assays - The enzyme-linked
 10 immuno-spot (ELISpot) assay was utilized to enumerate antigen-specific INF γ -secreting cells from mouse spleens (Miyahira, et al.1995, *J. Immunol. Methods* 181:45-54) or macaque PBMCs. Mouse spleens were pooled from 5 mice/cohort and single cell suspensions were prepared at 5×10^6 /mL in complete RPMI media (RPMI1640, 10% FBS, 2mM L-glutamine, 100U/mL Penicillin, 100 u/mL
 15 streptomycin, 10 mM Hepes, 50 uM β -ME). Rhesus PBMCs were prepared from 8-15 mL of heparinized blood following standard Ficoll gradient separation (Coligan, et al, 1998, *Current Protocols in Immunology*. John Wiley & Sons, Inc.). Multiscreen aqueous plates (Millipore, France) were coated with 100 μ L/well of either 5 μ g/mL purified rat anti-mouse IFN- γ IgG1, clone R4-6A2 (Pharmingen, San Diego, CA), or
 20 15 ug/mL mouse anti-human IFN- γ IgG_{2a} (Cat. No. 1598-00, R&D Systems, Minneapolis, MN) in PBS at 4°C overnight for murine or monkey assays, respectively. The plates were washed with PBS/penicillin/streptomycin and blocked with 200 μ L/well of complete RPMI media for 37 °C for at least 2 h.

To each well, 50 μ L of cell samples ($4-5 \times 10^5$ cells per well) and 50 μ L of the
 25 antigen solution were added. To the control well, 50 μ L of the media containing DMSO were added; for specific responses, either selected peptides or peptide pools (4 ug/mL per peptide final concentration) were added. For BALB/c mice immunized with the pol constructs, stimulation was conducted using a pool of CD4⁺-epitope containing 20-mer peptides (aa21-40, aa411-430, aa641-660, aa731-750, aa771-790)
 30 or a pool of CD8⁺-epitope containing peptides (aa201-220, aa311-330, aa781-800). For C57/BL6 mice immunized with the nef construct, either aa51-70 (CD8⁺ T cell epitope) or aa81-100 (CD4⁺) peptide derived from the nef sequence was added for specific stimulation. In monkeys, the responses against pol were evaluated using two pools (L and R) of 20-aa peptides that encompass the entire pol sequence and overlap
 35 by 10 amino acids. In monkeys vaccinated with the nef constructs, a single pool containing 20-mer peptides covering the entire HIV-1 nef sequence and overlapping

by 10 aa was used. Each sample/antigen mixture was performed in triplicate wells for murine samples or in duplicate wells for rhesus PBMCs. Plates were incubated at 37°C, 5% CO₂, 90% humidity for 20-24 h. The plates were washed with PBS/0.05% Tween 20 and incubated with 100 µL/well of either 1.25 µg/mL biotin-conjugated rat anti-mouse IFN-γ mAb, clone XMG1.2 (Pharmingen) or of 0.1 µg/mL biotinylated anti-human IFN-gamma goat polyclonal antibody (R&D Systems) at 4°C overnight. The plates were washed and incubated with 100 µL/well 1/2500 dilution of streptavidin-alkaline phosphatase conjugate (Pharmingen) in PBS/0.005% Tween/5% FBS for 30 min at 37 °C. Spots were developed by incubating with 100 µL/well 1-step NBT/BCIP (Pierce Chemicals) for 6-10 min. The plates were washed with water and allowed to air dry. The number of spots in each well was determined using a dissecting microscope and the data normalized to 10⁶ cell input.

Non-human Primate anti-RT ELISA - The pol-specific antibodies in the monkeys were measured in a competitive RT EIA assay, wherein sample activity is determined by the ability to block RT antigen from binding to coating antibody on the plate well. Briefly, Maxisorp plates were coated with saturating amounts of pol positive human serum (#97111234). 250 µL of each sample is incubated with 15 µL of 266 ng/mL RT recombinant protein (in RCM 563, 1% BSA, 0.1% tween, 0.1% NaN₃) and 20 µL of lysis buffer (Coulter p24 antigen assay kit) for 15 min at room temperature. Similar mixtures are prepared using serially diluted samples of a standard and a negative control which defines maximum RT binding. 200 µL/well of each sample and standard were added to the washed plate and the plate incubated 16-24 h at room temperature. Bound RT is quantified following the procedures described in Coulter p24 assay kit and reported in milliMerck units per mL arbitrarily defined by the chosen standard.

Results - Rodent Studies - BALB/c mice (n=5 mice/cohort) were immunized once or twice with varying doses of MRKAd5hCMV-IAPol(E3+) and MRKAd5hCMV-IAPol(E3-). At 3 weeks after the second dose, Anti-pol IgG levels were determined by an ELISA assay using RT as a surrogate antigen. Cellular response were quantified via IFNγ ELISpot assay against pools of pol-epitope containing peptides. The results of these assays are summarized in Table 10. The results indicate that the mouse vaccinees exhibited detectable anti-RT IgGs with an adenovector dose as low as 10⁷ vp. The humoral responses are highly dose-dependent and are boostable with a second immunization. One or two doses of either pol vectors elicit high frequencies of antigen-specific CD4⁺ and CD8⁺ T cells; the responses are weakly dose-dependent but are boostable with a second immunization.

Table 10. Immunogenicity of MRKAd5pol Vectors in BALB/c mice.

Group	Vaccine	Dose	No. of Doses	Anti-RT IgG Titers ^a			SFC/10 ⁶ cells ^b		
				GMT	+SE	-SE	Medium	CD4+ peptide pool	CD8+ peptide pool
1	MRKAd5hCMVFLpol (E3+)	10 ⁷ vp	2 1	310419 919	301785 372	153020 265	1(1) 1(1)	75(4) 72(9)	2313(87) 533(41)
2	MRKAd5hCMVFLpol (E3+)	10 ⁹ vp	2 1	1838400 ^b 713155	0 528520	0 303566	2(2) 1(1)	114(9) 48(7)	2083(182) 733(89)
3	MRKAd5hCMVFLpol (E3-)	10 ⁷ vp	2 1	310419 6400	386218 14013	172097 4393	0(0) 10(8)	223(7) 141(21)	2807(27) 409(28)
4	MRKAd5hCMVFLpol (E3-)	10 ⁹ vp	2 1	1838400 ^b 1241675 ^b	0 396725	0 300861	1(1) 0(0)	160(13) 39(13)	2385(11) 833(83)
5	Naïve	none	none	57	9	7	9(2)	11(4)	10(1)

^aGMT, geometric mean titer of the cohort of 5 mice; SE, standard error of the geometric mean^bNear or at the upper limit of the serial dilution; hence, could be greater than this value^cNo. of Spot-forming Cells per million splenocytes; mean values of triplicates are reported along with standard errors in parenthesis.

- 5 C57/BL6 mice were immunized once or twice with varying doses of MRKAd5hCMV-nef(G2A,LLAA) (E3+), MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10⁷ vp and (3) MRKAd5mCMV-tpanef(LLAA) (E3+) at either 10⁷ vp and 10⁹ vp. The immune response were analyzed using similar protocols and the results are listed in Table 11. While anti-nef IgG responses could not be detected in this
- 10 model system with any of the constructs, there are strong indications of a cellular immunity generated against nef using the ELIspot assay.

Table 11. Immunogenicity of MRKAd5nef Vectors in C57/BL6 mice.

Group	Vaccine	Dose	No. of Doses	Anti-nef IgG Titers ^a			SFC/10 ⁶ cells ^b		
				GMT	+SE	-SE	Medium	aa51-70 CD8+	aa81-100 CD4+
1	MRKAd5hCMVFLnef (E3+)	10 ⁷ vp	2 1	174 132	70 42	50 32	1(1) 0(0)	23(1) 0(0)	1(1) 0(0)
2	MRKAd5hCMVFLnef (E3+)	10 ⁹ vp	2 1	174 132	70 42	50 32	0(0) 1(1)	61(7) 62(7)	4(2) 3(1)
3	MRKAd5mCMVFLnef (E3+)	10 ⁷ vp	2 1	132 115	42 48	32 33	3(1) 3(2)	15(5) 3(2)	5(2) 4(2)
4	MRKAd5mCMVFLnef (E3+)	10 ⁹ vp	2 1	132 132	42 42	32 32	4(2) 2(1)	83(13) 29(2)	5(1) 4(0)
5	MRKAd5mCMVtpanef(E3+)	10 ⁷ vp	2 1	132 100	42 0	32 0	3(2) 3(1)	14(2) 13(4)	5(1) 10(3)
6	MRKAd5mCMVtpanef(E3+)	10 ⁹ vp	2 1	230 115	170 46	98 33	3(2) 7(1)	145(29) 151(14)	4(0) 10(0)
7	Naïve	none	none	152	78	62	21(2)	18(6)	28(3)

^aGMT, geometric mean titer of the cohort of 5 mice; SE, standard error of the geometric mean^bNo. of spot-forming cells per million splenocytes; mean values of triplicates are reported along with standard errors in parenthesis.

15

Monkey Studies - Cohorts of 3 rhesus macaques were immunized with 2 doses of MRKAd5hCMV-IApol(E3+) and MRKAd5hCMV-IApol(E3-). The number of antigen-specific T cells (per million PBMCs) were enumerated using one of two

- peptide pools (L and R) that cover the entire pol sequence; the results are listed in Table 12. Moderate-to-strong T cell responses were detected in the vaccinees using either constructs even at a low dose of 10^9 vp. Longitudinal analyses of the anti-RT antibody titers in the animals suggest that the pol transgene product is expressed efficiently to elicit a humoral response (Table 13). It would appear that generally higher immune responses were observed in animals that received the E3- construct compared to the E3+ virus.

Table 12. Pol-specific T Cell Responses in MRKAd5pol Immunized Rhesus

10 Macaques.

Vaccine (T=0,4 wks)	Monkey #	Prebleed			T=4			T=7			T=18		
		Mock	Pol L	Pol R	Mock	Pol L	Pol R	Mock	Pol L	Pol R	Mock	Pol L	Pol R
MRKAd5hCMV-IAPol(E3+) 10^{11} vp	99C100	1	0	0	1	38	31	0	52	146	0	49	715
	99C215	1	2	2	10	88	249	1	108	305	22	88	250
	99D201	5	5	4	6	149	85	0	40	35	0	35	18
MRKAd5hCMV-IAPol(E3+) 10^9 vp	99D212	0	2	0	4	331	114	0	58	14	0	6	6
	99D180	0	4	2	0	19	182	4	38	158	5	38	108
	99C201	8	5	21	6	62	62	0	18	32	1	14	65
MRKAd5hCMV-IAPol(E3-) 10^{11} vp	99D239	5	2	2	20	82	172	1	68	114	9	21	40
	99C186	4	12	6	5	120	421	2	271	489	16	875	530
	99C084	1	8	9	8	84	484	0	14	238	1	24	264
MRKAd5hCMV-IAPol(E3-) 10^9 vp	CC7C	10	10	8	12	724	745	4	322	378	4	188	176
	CD1G	2	0	1	5	474	468	0	232	212	0	101	121
	CD11	6	6	12	10	98	110	5	60	80	8	25	34
Naive	083Q	nd	nd	nd	nd	nd	nd	4	2	2	2	1	2

nd, not determined
Reported are SFC per million PBMCs; mean of duplicate wells.

Table 13. Anti-RT Ig Levels in MRKAd5pol Immunized macaques.

RT ANTIBODY ASSAY TITERS IN mMU/mL				
Vaccine/Monkey Tag	T=4	T=7	T=12	T=16
MRKAd5hCMV-IAPol(E3+), 10^{11} vp				
99C100	61	1999	5928	4768
99C215	81	1541	2356	2767
99D201	53	336	539	387
MRKAd5hCMV-IAPol(E3+), 10^9 vp				
99D212	10	40	49	68
99D180	<10	36	79	93
99C201	<10	37	71	76
MRKAd5hCMV-IAPol(E3-), 10^{11} vp				
99D239	44	460	1234	1015
99C186	21	233	480	345
99C084	235	2637	2858	1626
MRKAd5hCMV-IAPol(E3-), 10^9 vp				
CC7C	32	175	306	235
CD1G	20	140	273	419
CD11	15	112	149	237

When rhesus macaques were immunized i.m. with two doses of MRKAd5nef constructs, vigorous T cell responses ranging from 100 to as high as 1100 per million were observed in 8 of 12 vaccinees (Table 14). The efficacies of the mCMV- and hCMV- driven nef constructs are comparable on the basis of the data generated thus far.

10 Table 14. Nef-specific T cell Responses in MRKAd5nef Immunized Rhesus Macaques.

Vaccine (T=0,4 wks)	Monk #	Pre		T=4		T=7		T=16	
		Mock	Nef	Mock	Nef	Mock	Nef	Mock	Nef
MRKAd5hCMV-nef(G2A,LLAA) (E3+) 10 ¹¹ vp	CD2D	0	4	31	440	4	368	1	251
	CC7B	0	0	2	521	0	178	1	1522
	CC61	2	9	31	112	0	108	11	100
MRKAd5hCMV-nef(G2A,LLAA) (E3+) 10 ⁹ vp	CC2K	9	9	6	52	0	35	0	16
	CD15	5	4	30	998	2	588	0	434
	CD16	6	1	8	1148	0	369	1	212
MRKAd5mCMV-nef(G2A,LLAA) (E3+) 10 ¹¹ vp	99D191	1	5	4	614	0	298	2	419
	99D144	4	6	5	434	0	1100	2	932
	99C193	1	2	1	58	1	22	0	64
MRKAd5mCMV-nef(G2A,LLAA) (E3+) 10 ⁹ vp	99D224	1	11	14	231	1	125	0	70
	99D250	8	9	4	108	0	54	0	5
	99C120	1	6	20	299	0	92	0	79
Naive	083Q	nd	nd	18	22	4	5	2	1

EXAMPLE 25

15 Comparison of Clade B vs. Clade C T Cell Responses in HIV-Infected Subjects

PBMC samples collected from two dozens of patients infected with HIV-1 in US were tested in ELISPOT assays with peptide pools of 20-mer peptides overlapping by 10 amino acids. Four different peptide pools were tested for cross-clade recognition, and they were either derived from a clade B-based isolate (gag H-b; nef-

20 b) or a clade C-based isolate (gag H-c, nef-c). Data in Table 15 shows that T cells from these patients presumably infected with clade B HIV-1 could recognize clade C gag and nef antigens in ELISPOT assay. Correlation analysis further demonstrated that these T cell responses against clade C gag peptide pool were about 60% of the clade B counterpart (Figure 24), while the T cell responses against clade C nef were

25 about 85% of the clade B counterpart (Figure 25). These results suggest that cellular immune responses generated in patients infected with clade B HIV-1 can recognize gag and nef antigens derived from clade C HIV-1. These data show that a HIV vaccine, such as a DNA or MRKAd5-based adenoviral vaccine expressing a clade B

gag and/or nef antigen will potentially have the ability to provide a prophylactic and/or therapeutic advantage on a global scale.

5

Table 15
Responses Shown as the Number of gIFN-Secreting T Cells per Million PBMCs

subject	bleed date	gag epitope # (from mapping)	mock	gag H-b	gagH-c	nef-b	nef-c
#100	19-Jul-99	12	10	3950	1385	1295	1300
#101	25-Jul-99	3	15	3885	1280	na	1020
#102	25-Jul-99	4	15	1740	850	1255	1785
#104	7-Jun-99	2	5	1355	1185	na	1060
#107	11-Oct-99	2	25	3305	2795	670	870
#405	11-Jul-99	2	15	4575	3180	1700	1500
#501	19-Jul-99	2	15	1100	570	3365	3460
#505	18-Jul-99	5	10	2145	1725	1235	na
#506	28-Feb-99	2	25	150	45	400	610
#701	28-Mar-99	5	30	7620	4775	3320	2780
#709	17-May-99	3	15	2785	1945	1090	1630
#710	24-May-99	4	5	1055	1080	2210	2140

10

EXAMPLE 26

Characterization and Production of MRKAd5pol and MRKAd5nef Vectors in Roller Bottles

Expansion of nef and pol Adenovectors - Nef and pol CsCl purified MRKAd5 seeds were used to infect roller bottles to produce P4 virus to be used as a seed for further experiments. P4 MRKAd5 pol and nef vectors were used to infect roller bottles at an MOI 280 vp/cell, except for hCMV-tpa-nef [E3+] which was infected at an MOI of 125 due to low titers of seed obtained at P4.

20

Table 16 Viral particle concentrations for P5 nef and pol adenovectors

Adenovector	AEX Titer (10 ¹⁰ vp/ml culture)	AEX Titer (10 ⁴ vp/cell)	Amplification Ratio
hCMV-FL-nef [E3+]	1.1	0.9	30
mCMV-FL-nef [E3+]	2.2	2.1	75
hCMV-tpa-nef [E3+]	0.07	0.1	5
mCMV-tpa-nef [E3+]	1.3	0.9	35
hCMV-FL-pol [E3+]	2.7	2.1	75
hCMV-FL-pol [E3-]	1.9	1.3	45

- 5 *Roller Bottle Passaging* - Passaging of the *pol* and *nef* constructs continued through passage seven. Cell-associated (freeze/thaw lysis) and whole broth (triton-lysis) titers obtained in all passages were very consistent. In general, MRKAd5pol is ca. 70% as productive as MRKAd5gag while MRKAd5nef is ca. 25% as productive as MRKAd5gag. Samples of P7 virus for both constructs were analyzed by V&CB by
- 10 restriction digest analysis and did not show any rearrangements.

Table 17. Passage Six Viral Productivity for MRKAd5pol and MRKAd5nef

		Xviable (10 ⁶ cells/ml), Viability (%)		Cell Passage Number	ABX Titer (Cell Associated) 10 ¹⁰ vp/ml culture	Titer 10 ⁴ vp/cell	Amplification Ratio	Triton Lysis Titer 10 ¹⁰ vp/ml culture
		Infection	Harvest					
hCMV-FL-nef [E3+]	pool	1.22, 85%		62	0.8	0.7	25	1.6
	1		0.99, 62%					
	2		1.10, 72%					
hCMV-FL-pol [E3+]	pool	1.42, 89%		62	4.5	3.2	115	7.0
	1		1.22, 70%					
	2		1.42, 74%					

15 Table 18. Passage Seven Viral Productivity for MRKAd5pol and MRKAd5nef

		Xviable (10 ⁶ cells/ml), Viability (%)		Cell Passage Number	ABX Titer (Cell Associated) 10 ¹⁰ vp/ml culture	Titer 10 ⁴ vp/cell	Amplification Ratio	Triton Lysis Titer 10 ¹⁰ vp/ml culture
		Infection	Harvest					
hCMV-FL-nef [E3+]	Pool	1.33, 90%		66	1.0	0.8	29	2.1
	1		0.96, 70%					
	2		1.18, 73%					
hCMV-FL-pol [E3+]	Pool	0.90*, 90%		56	4.2	4.7	168	6.5
	1		1.18, 88%					
	2		1.04, 80%					

- MRKAd5nef and MRKAd5pol Viral Production Kinetics* - A timecourse experiment was carried out in roller bottles to determine if the viral production kinetics of the MRKAd5pol and MRKAd5nef vectors were similar to those of
- 20 MRKAd5gag. PER.C6[®] cells in roller bottle cultures were infected at an MOI of 280 vp/cells with P5 MRKAd5pol, P5 MRKAd5nef and P7 MRKAd5gag; for each adenovector, two infected bottles were sampled at 24, 36, 48, and 60 hours post infection. In addition, two bottles were left unsampled until 48 hpi when they were
- 25 harvested under the Phase I process conditions. The anion-exchange HPLC viral particle concentrations of the freeze-thaw recovered cell associated virus at the 24, 36,

48, and 60 hpi timepoints are shown in Figure 29A-B. The QPA titers show a similar trend (data not shown).

- 5 *Comparison of hCMV- and mCMV-FL-nef* - As the titers obtained with the MRKAd5nef construct (hCMV-FL-nef) were lower than those obtained with MRKAd5gag or MRKAd5pol, a viral productivity comparison experiment was performed with mCMV-FL-nef. For each of the two adenovectors (hCMV- and mCMV-FL-nef), two roller bottles were infected at an MOI of 280 vp/cell with passage five clarified lysate. The macroscopic and microscopic observations of the
- 10 four roller bottles were identical at the time of harvest. Analysis of the clarified lysate produced indicated a higher viral particle concentration in the bottles infected with mCMV-FL-nef, as shown in Table 19. It is stipulated that the higher productivity with mCMV promoter driven nef vector is due to lower nef expression levels in PER.C6[®] cells- experiments are underway at V&CB to measure nef expression levels.

15

Table 19. Passage Six Viral Productivity Comparison of hCMV- and mCMV-FL-nef

		Xv (10 ⁶ cells/ml), Viability (%)		Cell Passage	AEX Titer	Titer	Amplification	Triton Lysis Titer
		Infection	Harvest	Number	10 ¹⁰ vp/ml culture	10 ⁶ vp/cell	Ratio	10 ¹⁰ vp/ml culture
hCMV-FL-nef (MRKAd5nef)	Pool	1.11, 91%		60	1.5	1.4	50	2.8
	1		1.23, 75%					
	2		1.34, 74%					
mCMV-FL-nef	Pool	1.11, 91%		60	2.3	2.1	75	4.6
	1		1.49, 84%					
	2		1.18, 77%					

20

EXAMPLE 27

Characterization and Large Scale Production of MRKAd5nef Virus in Bioreactors

- Materials and Methods* - The experiment of the present example was run twice under the following conditions: 36.5°C, DO 30%, pH 7.30, 150rpm agitation rate,
- 25 no sparging, Life Technologies (Gibco, Invitrogen) 293 SFM II (with 6mM L-glutamine), 0.5M NaOH as base for pH control. During the first run (B20010115), two 10L stirred vessel bioreactors were inoculated with PER.C6[®] cells at a concentration of 0.2x10⁶ cells/ml. Cells were grown until they reached a cell concentration of approximately 1x10⁶ cells/ml. The cells were infected with uncloned
- 30 MRKAd5nef (G2A,LLAA) at a MOI of 280 virus particles (vp)/cell. For the second batch (B20010202), the same procedure as the first run was used, except the cells

- were infected with cloned MRAd5nef. During both runs, the bioreactors were harvested 48 hours post-infection. Samples were taken and virus concentrations were determined from whole broth (with triton lysis), supernatant, and cell pellets (3 X freeze/thaw) with the AEX and QPA assays. Metabolites were measured with BioProfile 250 throughout the process.

Table 20: Experimental Conditions

Temperature	36.5 °C
DO	30%
PH	7.30
Agitation	150 rpm
Sparging	None

Table 21: Virus source used for experiments.

10

Run	Batch ID	Cloned/Unclosed MRKAd5nef	MOI (vp/cells)
#1	B20010115-1	Unclosed	280
	B20010115-2	Unclosed	280
#2	B20010202-1	Cloned	280
	B20010202-2	Cloned	280

Results - Table 22 and 23 show an the ability to scale up production of MRKAd5nef by growth in a bioreactor.

15

Table 22: Virus Concentration as measured by the AEX assay

Run	Batch ID	Cloned/Unclosed MRKAd5nef	Virus Concentration @ 48hpi (1x10 ¹³ vp/L)			
			Supernatant	Clarified Lysate	Total	Triton Lysate
#1	B20010115-1	Unclosed	0.72	3.26	3.98	5.76
	B20010115-2	Unclosed	0.38	1.67	2.05	2.46
#2	B20010202-1	Cloned	0.80	6.00	6.80	8.88
	B20010202-2	Cloned	0.50	6.00	6.50	8.47

Table 23: Virus Titers as measured by the QPA assay

Run	Batch ID	Cloned/Unclosed MRKAd5nef	Virus Concentration @ 48hpi (1x10 ¹¹ IU/L)				
			Whole Broth	Supernatant	Clarified Lysate	Total	Triton Lysate
#1	B20010115-1	Unclosed	0.13	1.12	1.76	2.88	11.28
	B20010115-2	Unclosed	0.14	0.73	1.54	2.27	5.86
#2	B20010202-1	Cloned	0.14	0.97	1.62	2.69	11.89
	B20010202-2	Cloned	0.14	1.17	1.70	2.97	12.47

20

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art

from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

EXAMPLE 28

MRKAd5HIV-1gag Boosting of DNA-Primed Animals

5 Groups of 3-5 rhesus macaques were immunized with (a) 5 mgs of V1Jns-Flgag (pV1JnsCMV(no intron)-FL-gag-bGHpA), (b) 5 mgs of V1Jns-Flgag formulated with 45 mgs of a non-ionic block copolymer CRL1005, or (c) 5 mgs of
10 V1Jns-Flgag formulated with 7.5 mgs of CRL1005 and 0.6 mM benzalkonium chloride at weeks 0, 4, and 8. All animals received a single dose of 10^7 viral particles (vp) of the MRKAd5HIV-1gag at week 26. Note: 10^7 is too low to prime or boost effectively when used as a single modality (dose is selected to mimic preexposure to adenovirus); see Figure 32.

15 Blood samples were collected from all animals at several time points and peripheral blood mononuclear cells (PBMCs) were prepared using standard Ficoll method. The PBMCs were counted and analyzed for gamma-interferon secretion using the ELISpot assay (Table 24). For each monkey, the PBMCs were incubated overnight either in the absence (medium) or presence of a pool (called "gag H") of 50
20 20-aa long peptides that encompass the entire HIV-1 gag sequence.

The results indicate that MRKAd5HIV-1gag was very effective in boosting the T cell immune responses in these monkeys. At week 28 or 2 weeks after the viral boost, the number of gag-specific T cells per million PBMCs increased 2-48 fold compared to the levels observed at week 24 or 2 weeks prior to the boost.

25 The PBMCs were also analyzed by intracellular gamma-interferon staining prior to (at week 10) and after the MRKAd5gag boost (at week 30). The results for select animals are shown on Figure 31. The results indicate that (a) immunization with DNA/adjuvant formulation elicited T cell responses which can either be balanced, $CD4^+$ -biased or $CD8^+$ -biased, and (b) boosting with the MRKAd5gag
30 construct produced in all cases a strongly $CD8^+$ -biased response. These results suggest that boosting with MRKAd5HIV-1gag construct is able to improve the levels of antigen-specific $CD8^+$ T cells.

Table 24. Boosting of DNA/Adjuvant-Primed Rhesus Monkeys with MRKAd5gag

Grp	Priming T=0, 4, 8 wks DNA/5 mgs PBS (D101)	Boost T=28 wks MRKAd5gag(E3+) 10 ⁷ vp	Month	T=0			T=4			T=6			T=10			T=17			T=24			T=28			T=30		
				Medium	gag H	gag H	Medium	gag H	gag H	Medium	gag H	gag H	Medium	gag H	gag H	Medium	gag H	gag H	Medium	gag H	gag H	Medium	gag H	gag H	Medium	gag H	gag H
1			CB5H CB5K PBS (D101)	NA 0 6	NA 0 11	35 15 36	3 0 0	35 15 36	3 0 0	15 0 51	15 0 51	71 48 51	4 0 3	224 58 48	8 0 2	115 76 89	8 0 8	05 35 65	05 35 65	19 3 10	556 1705 989	19 3 10	556 1705 989	0 1 0	316 755 395	0 1 0	
2			DNA/5 mgs + CRL 1005/45 mgs	CC1C CC1K AW3P CB5F AW8B	0 4 9 9 9	4 0 8 NA 12	60 101 10 31 38	1 1 1 0 4	60 101 10 31 38	1 1 1 0 4	111 254 71 268 119	0 0 4 0 1	111 254 71 268 119	5 4 4 0 0	270 781 164 530 439	4 5 8 19 0	280 452 104 374 425	4 5 8 19 0	232 321 85 251 316	8 0 5 9 0	3 0 11 8 4	559 1915 836 1349 1229	3 0 11 8 4	559 1915 836 1349 1229	19 1 8 20 5	1345 1099 241 1734 1354	19 1 8 20 5
3			DNA/5 mgs + CRL 1005/7.5 mgs + 0.6 mM BAK	AW2D CA4R CB5B CB5W CB7D	10 1 8 4 1	4 0 8 3 0	59 121 6 26 136	1 3 0 0 0	59 121 6 26 136	1 3 0 0 0	284 135 119 91 316	5 1 3 1 0	284 135 119 91 316	19 1 0 0 1	425 270 274 139 609	6 5 8 0 5	105 130 282 184 628	9 1 1 1 5	205 105 208 82 759	9 1 1 1 5	18 14 0 5 0	565 1384 638 543 2278	18 14 0 5 0	565 1384 638 543 2278	8 10 1 1 4	404 978 828 349 1831	8 10 1 1 4
4	none	None	98D201	3	0	0	0	0	0	1	0	0	0	0	0	1	1	2	3	0	0	0	0	0	0	0	
NA not available																											

NA, not available

EXAMPLE 29

Construction of gagpol fusion for MRKAd5gagpol fusion constructs

5 The open reading frames for the codon-optimized HIV-1 gag gene was fused directly to the open reading frame of the LA pol gene (consisting of RT, RNaseH and integrase domains) by stepwise PCR. Because the gene (SEQ ID NO: 38) does not include the protease gene and the frameshift sequence, it encodes a single polypeptide of the combined size of p55, RT, RNase H and integrase (1350 amino acids; SEQ ID NO: 39).

10 The fragment that extends from the BstEII site within the gag gene to the last non-stop codon was ligated via PCR to a fragment that extends from the start codon of the LApol to a unique BamHI site. This fragment was digested with BstEII and BamHI. Construction of gag-LApol fusion was achieved via three-fragment ligation involving the PstI-BstEII gag digestion fragment, the BstEII/BamHI digested PCR
15 product and long PstI/BamHI V1R-FLpol backbone fragment.

The MRKAd5-gagpol adenovirus vector was constructed using the BglII fragment of the V1R-gagpol containing the entire ORF of gag-LApol fusion gene.

EXAMPLE 30

20 Immunogenicity Studies in Non-Human Primates

Cohorts of three (3) macaques were immunized with 10e8 or 10e10 viral particles (vp) of one of the following MRKAd5 HIV-1 vaccines: (1) MRKAd5gag; (2) MRKAd5pol; (3) MRKAd5nef; (4) a mixture containing equal amounts of
25 MRKAd5gag, MRKAd5pol, and MRKAd5nef, or (5) a mixture of equal amounts of MRKAd5gagpol and MRKAd5nef. The vaccines were administered at weeks 0 and 4.

The T cell responses against each of the HIV-1 antigens were assayed by IFN-gamma ELISpot assay using pools of 20-aa peptides that encompass the entire protein
30 sequence of each antigen. The results (Table 25) are expressed as the number of spot-forming cells (sfc) per million peripheral blood mononuclear cells (PBMC) that respond to each of the peptide pools.

Results indicate the following observations: (1) each of the single gene constructs (MRKAd5gag, MRKAd5pol, or MRKAd5nef) is able to elicit high levels
35 of antigen-specific T cells in monkeys; (2) the single-gene MRKAd5 constructs can be mixed as a multi-cocktail formulation capable of eliciting very broad T cell responses against gag, pol, and nef; (3) the MRKAd5 vector expressing the fusion

protein of gag plus IA pol is capable of inducing strong T cell responses to both gag and pol.

Table 25. Evaluation of Mixtures of MRKAd5 vectors expressing humanized HIV-1 gag, pol, gagpol, nef in rhesus macaques

Grp #	Vaccine T=0, 4 wks	Monk #	T=6 wks				
			Mock	Gag H	Pol - 1	Pol - 2	Nef
1	MRKAd5 gag 10 ¹⁰ vp	CB9V	0	15	-	-	-
		CD19	0	374	-	-	-
		109H	1	843	-	-	-
2	MRKAd5 gag 10 ⁸ vp	99D130	1	948	-	-	-
		W277	16	324	-	-	-
		143H	4	595	-	-	-
3	MRKAd5 pol 10 ¹⁰ vp	CC1X	4	-	46	256	-
		AW3W	3	-	463	550	-
		AV43	6	-	95	1333	-
4	MRKAd5 pol 10 ⁸ vp	AW38	1	-	19	30	-
		CC8K	0	-	50	995	-
		CC21	1	-	33	436	-
5	MRKAd5 nef 10 ¹⁰ vp	076Q	9	-	-	-	1204
		091Q	4	-	-	-	85
		083Q	0	-	-	-	176
6	MRKAd5 nef 10 ⁸ vp	00C029	1	-	-	-	114
		98D022	6	-	-	-	170
		98D160	3	-	-	-	198
7	MRKAd5gag+MRKAd5pol+MRKAd5nef 10 ¹⁰ vp each	99D251	3	206	15	193	120
		05H	3	135	21	9	638
		00C016	3	26	4	51	23
8	MRKAd5gag+MRKAd5pol+MRKAd5nef 10 ⁸ vp each	99D215	1	171	18	193	240
		81H	5	73	6	14	243
		12H	8	1140	115	811	719
9	MRKAd5gagpol +MRKAd5 nef 10 ¹⁰ vp each	99D211	0	83	56	838	725
		22H	4	385	119	1194	1915
		61H	4	343	11	765	853
10	MRKAd5gagpol +MRKAd5 nef 10 ⁸ vp each	34H	3	78	19	5	75
		48H	1	65	105	46	43
		70H	5	158	15	220	191

Indicated are numbers of spot-forming cells per million PBMCs against the peptide pools. Mock, no peptides; gag H, fifty 20-aa peptides encompassing p55 sequence; pol-1, 20-aa peptides representing N-terminal half of IA pol; pol-2, 20-aa peptides representing the carboxy-terminal half of IA pol; nef, 20-aa peptides encompassing the entire wild-type nef sequence. Responses to the antigens prior to the first immunization did not exceed 40 sfc/10⁶ PBMC.

WHAT IS CLAIMED IS

1. A recombinant adenoviral vaccine vector at least partially deleted in
5 E1 and devoid of E1 activity, comprising:
- a) an adenovirus *cis*-acting packaging region corresponding to from
about base pair 1 to between from about base pair 400 to about
base pair 458 of a wildtype adenovirus genome; and
 - b) a gene encoding an HIV protein or immunologically relevant
10 modification thereof.
2. A vector in accordance with claim 1 comprising a packaging region
corresponding to from about base pair 1 to about base pair 450 of a wildtype
adenovirus genome.
3. A vector in accordance with claim 1 further comprising nucleotides
15 corresponding to between from about base pair 3511 to about 3524 to about base pair
5798 of a wildtype adenovirus genome.
4. A vector in accordance with claim 3 comprising base pairs
corresponding to 1-450 and 3511-5798 of a wildtype adenovirus genome.
5. A vector in accordance with claim 4 which is deleted of base pairs
20 451-3510.
6. A vector in accordance with claim 1 which is at least partially
deleted in E3.
7. A vector in accordance with claim 6 wherein the E3 deleted region
is from base pairs 28,133-30,818.

8. A vector in accordance with claim 1 wherein the gene encoding the HIV protein or modification thereof comprises codons optimized for expression in a human.

9. A vector in accordance with claim 1 wherein the vector comprises a
5 gene expression cassette comprising:

a) a nucleic acid encoding a protein;

b) a heterologous promoter operatively linked to the nucleic acid encoding the protein; and

(c) a transcription termination sequence.

10 10. A vector in accordance with claim 9 wherein the gene expression cassette is inserted into the E1 region.

11. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette is in an E1 parallel orientation

12. An adenoviral vector in accordance with claim 9 wherein the gene
15 expression cassette is in an E1 antiparallel orientation.

13. An adenoviral vector in accordance with claim 9 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

14. An adenoviral vector in accordance with claim 13 wherein the promoter is an immediate early human cytomegalovirus promoter.

20 15. An adenoviral vector in accordance with claim 9 wherein the promoter is a murine cytomegalovirus promoter.

16. An adenoviral vector in accordance with claim 9 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

17. An adenoviral vector in accordance with claim 9 wherein the transcription termination sequence is a synthetic polyadenylation signal (SPA).

18. A cell comprising the adenoviral vector of claim 1.

19. Recombinant, replication-defective adenovirus particles harvested
5 and purified subsequent to transfection of the adenoviral vector of claim 1 into a cell line which expresses adenovirus E1 protein at complementing levels.

20. An HIV vaccine composition comprising purified adenovirus particles of claim 19.

21. An HIV vaccine composition of claim 20 which comprises a
10 physiologically acceptable carrier.

22. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 1 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant,
15 replication-defective adenovirus.

23. A method according to claim 22 wherein the cell is a PER.C6[®] cell.

24. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of
20 claim 21.

25. A method according to claim 24 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

26. A method according to claim 25 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

27. A method according to claim 24 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

28. A method according to claim 24 which comprises administering and readministering the adenovirus vaccine vector to the individual.

29. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV gag or an immunologically relevant modification thereof.

30. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV gag protein or immunologically relevant modification thereof.

31. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

- a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and
- b) a gene expression cassette comprising
 - i) SEQ ID NO: 29;
 - ii) a heterologous promoter operatively linked to i); and
 - iii) a transcription termination sequence.

32. An adenoviral vector in accordance with claim 31 wherein the gene expression cassette is in an E1 parallel orientation.

33. An adenoviral vector in accordance with claim 31 wherein the gene expression cassette is in an E1 antiparallel orientation.

5 34. An adenoviral vector in accordance with claim 31 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

35. An adenoviral vector in accordance with claim 31 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

10 36. An adenoviral vector in accordance with claim 31 which is at least partially deleted in E3.

37. A cell comprising the adenoviral vector of claim 30.

38. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 30 into a cell
15 line which expresses adenovirus E1 protein at complementing levels.

39. An HIV vaccine composition comprising purified adenovirus particles of claim 38.

40. An HIV vaccine composition of claim 39 which comprises a physiologically acceptable carrier.

20 41. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 30 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

42. A method according to claim 41 wherein the cell is a PER.C6[®] cell.

43. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of
5 claim 21.

44. A method according to claim 43 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

10 45. A method according to claim 44 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

46. A method according to claim 43 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

15 47. A method according to claim 43 which comprises administering and readministering the adenovirus vaccine vector to the individual.

48. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV pol or an immunologically relevant modification thereof.

20 49. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV pol protein or immunologically relevant modification thereof.

50. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

- 5 a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and
- b) a gene expression cassette comprising
- i) a nucleotide sequence selected the group consisting of SEQ ID NO: 1, SEQ ID NO: 5 and SEQ ID NO: 7;
 - ii) a heterologous promoter operatively linked to i); and
 - 10 iii) a transcription termination sequence.

51. An adenoviral vector in accordance with claim 50 wherein the gene expression cassette is in an E1 parallel orientation.

52. An adenoviral vector in accordance with claim 50 wherein the gene expression cassette is in an E1 antiparallel orientation.

15 53. An adenoviral vector in accordance with claim 50 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

54. An adenoviral vector in accordance with claim 50 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

20 55. An adenoviral vector in accordance with claim 50 which is at least partially deleted in E3.

56. A cell comprising the adenoviral vector of claim 49.

57. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 49 into a cell line which expresses adenovirus E1 protein at complementing levels.

58. An HIV vaccine composition comprising purified adenovirus
5 particles of claim 57.

59. An HIV vaccine composition of claim 58 which comprises a physiologically acceptable carrier.

60. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of
10 claim 49 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

61. A method according to claim 60 wherein the cell is a PER.C6[®] cell.

15 62. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of claim 59.

63. A method according to claim 62 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with
20 a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

64. A method according to claim 63 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

65. A method according to claim 62 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

66. A method according to claim 62 which comprises administering and readministering the adenovirus vaccine vector to the individual.

5 67. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV nef or an immunologically relevant modification thereof.

68. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV nef protein or immunologically relevant modification thereof.

10 69. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs
15 corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and

b) a gene expression cassette comprising

i) a nucleotide sequence selected the group consisting of
SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13 and
20 SEQ ID NO: 15;

ii) a heterologous promoter operatively linked to i); and

iii) a transcription termination sequence.

70. An adenoviral vector in accordance with claim 69 wherein the gene expression cassette is in an E1 parallel orientation.

71. An adenoviral vector in accordance with claim 69 wherein the gene expression cassette is in an E1 antiparallel orientation.

72. An adenoviral vector in accordance with claim 69 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

5 73. An adenoviral vector in accordance with claim 69 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

74. An adenoviral vector in accordance with claim 69 which is at least partially deleted in E3.

10 75. A cell comprising the adenoviral vector of claim 68.

76. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 68 into a cell line which expresses adenovirus E1 protein at complementing levels.

15 77. An HIV vaccine composition comprising purified adenovirus particles of claim 76.

78. An HIV vaccine composition of claim 77 which comprises a physiologically acceptable carrier.

20 79. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 68 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

80. A method according to claim 79 wherein the cell is a PER.C6[®] cell.

81. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of claim 78.

82. A method according to claim 81 which further comprises
5 administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

83. A method according to claim 82 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus
10 vaccine.

84. A method according to claim 81 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

85. A method according to claim 81 which comprises administering and readministering the adenovirus vaccine vector to the individual.

15 86. A multivalent adenovirus vaccine composition comprising recombinant, replication-defective adenovirus particles, wherein the adenovirus particles are harvested and purified from a cell line expressing adenovirus E1 protein, and wherein the particles are harvested subsequent to transfection of the cells with an adenoviral vector or vectors in accordance with claim 9; said vector(s) comprising a
20 gene expression cassette or cassettes comprising nucleotide sequences encoding HIV proteins selected from the group consisting of:

- a) gag, pol, and nef, expressed independently from three individual vectors;

- 5
- b) gag, pol, and nef, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- c) gag, pol, and nef, expressed via two vectors, one expressing a pol-nef fusion, and another expressing gag;
- d) gag, pol, and nef, expressed via two vectors, one expressing a gag-pol fusion and another expressing nef;
- e) gag, pol and nef, expressed via two vectors, one expressing a nef-gag fusion and another expressing pol;
- 10
- f) gag, pol, and nef, expressed via one vector expressing a gag-pol-nef fusion;
- g) gag and pol, expressed independently from two individual vectors;
- h) gag and pol, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- 15
- i) pol and nef, expressed independently from two individual vectors;
- j) pol and nef, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- 20
- k) nef and gag, expressed independently from two individual vectors;
- l) nef and gag, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- m) gag and pol, expressed via one vector expressing a gag-pol fusion;

n) pol and nef, expressed via one vector expressing a pol-nef fusion;

and

o) nef and gag, expressed via one vector expressing a nef-gag fusion.

87. A multivalent adenovirus vaccine composition in accordance with
5 claim 86 wherein the gag-pol fusion consists of SEQ ID NO: 39.

88. A multivalent adenovirus vaccine composition in accordance with
claim 86 wherein the fused sequences have the encoding nucleic acid sequences
operatively linked to distinct promoters and transcription termination sequences.

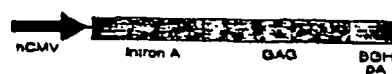
89. A multivalent adenovirus vaccine composition in accordance with
10 claim 86 wherein the fused sequences have the encoding nucleic acid sequences
operatively linked to a single promoter; and the encoding nucleic acid sequences
operatively linked by an internal ribosome entry sequence ("IRES").

Sequence of the open reading frame for FL-gag (human codon optimized)

atgggtgctagggctctgtgctgtctgggtgagctggacaagtgggagaagatcaggctgaggccctgggtg
caagaagaagtacaagctaaagcacatgtgtgggctccaggagctggagaggtttgtgtgaacctggc
ctgtggagacctctgaggggtgcaggcagatcctgggccaagctccagccctccctgcaaacaggctctgagg
agctgaggctccctgtacaacacagtggttacctgtactgtgtgcaccagaagattgatgtgaaggacaccaag
gaggccctggagaagaattgaggaggagcagaacaagtccaagaagaaggcccagcaggctgtgtgtggc
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ggatgacagagaccctgtgtgtgcagaatgccaaacctgactgcaagaccatccgaaggccctgggcccctg
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cccgaggagtcctcagggttggggaggagaagaccacccccagccagaagcaggagcccatgacaagg
agctgtacccccctggcctccctgagggtccctgttggcaacgacccctctccaglaaaaataaagcccgggca
gat (SEQ ID NO: 29)

Figure 2

Old Transgene:



New Transgenes:

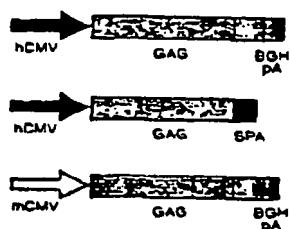


Figure 3: Diagrammatic representation of the original HIV-1 gag transgene and the series of new transgene constructions.

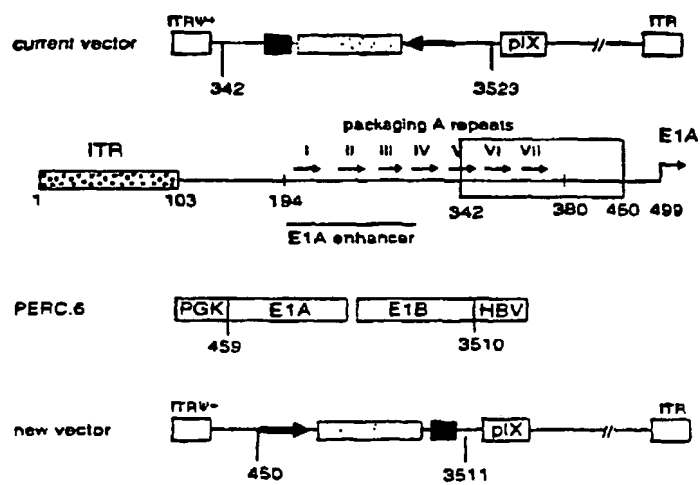


Figure 4: Modifications made to the current adenovector backbone in the generation of the new vector.

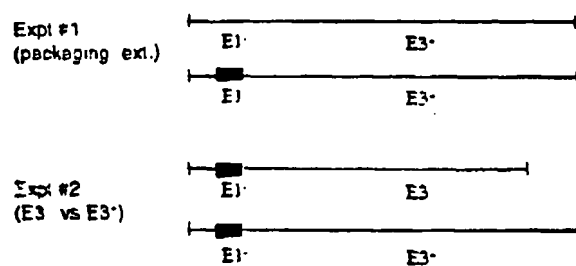


Figure 5: Virus mixing experiments to determine the effects of the addition made to the packaging signal region (Expt #1) and analysis of the effects of the E3 gene on viral growth (Expt. #2). The red bars denote the region of modifications made to the E1 deletion.

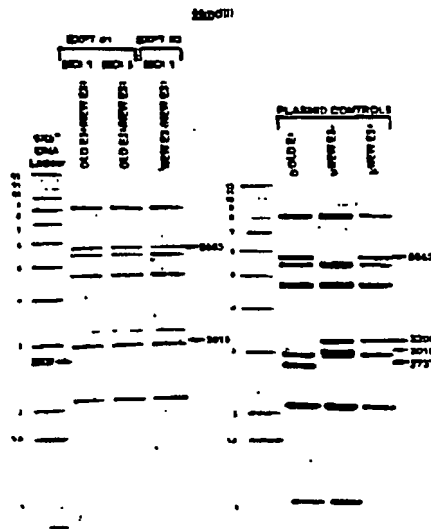


Figure 6: Autoradiograph of viral DNA analysis following viral mixing experiments (expts. #1 and #2) as detailed in the text.

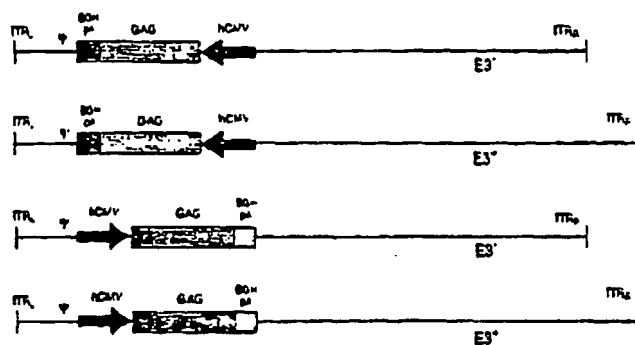


Figure 7A: hCMV-FLgag-bGHpA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3- and E3+ backbones were constructed.

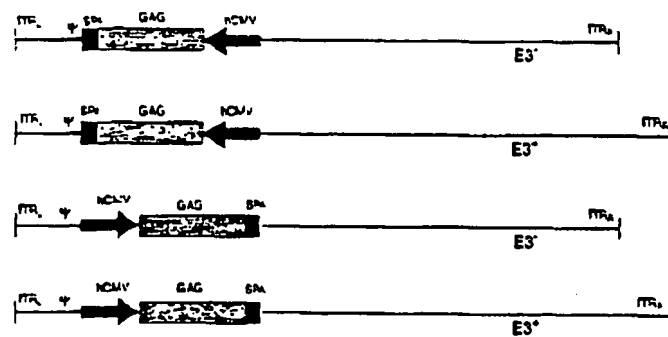


Figure 7B: hCMV-FLgag-SPA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3⁻ and E3⁺ backbones were constructed.

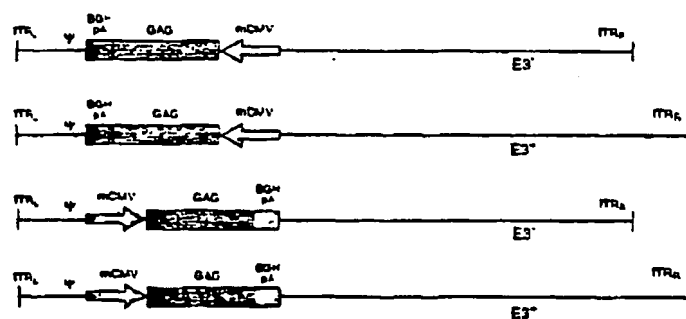


Figure 7C: mCMV-FLgag-bGHpA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3⁻ and E3⁺ backbones were constructed.

Plasmid mixing expt: (orientation)

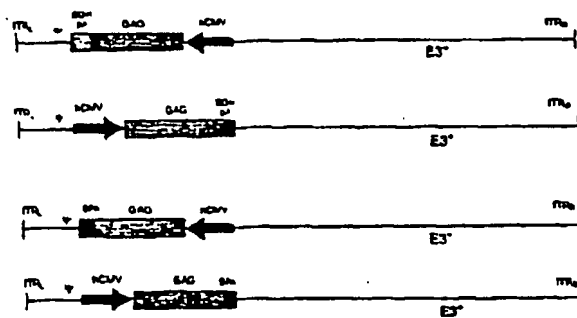


Figure 8A: Effect of transgene orientation

Plasmid Mixing expt: (poly A signal)

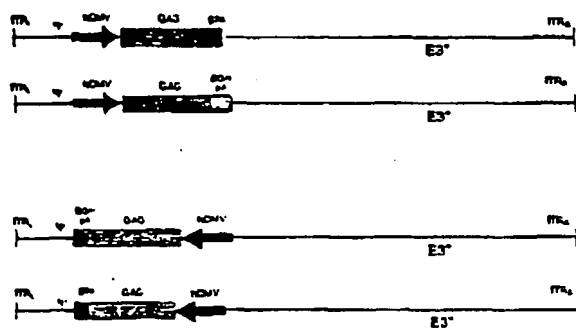


Figure 8B: Effect of polyadenylation signal

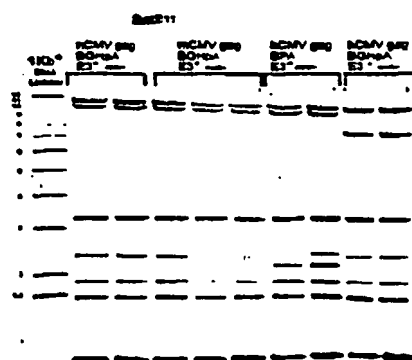


Figure 9: Viral DNA from the four Adgag candidates at P5, following BstE11 digestion.

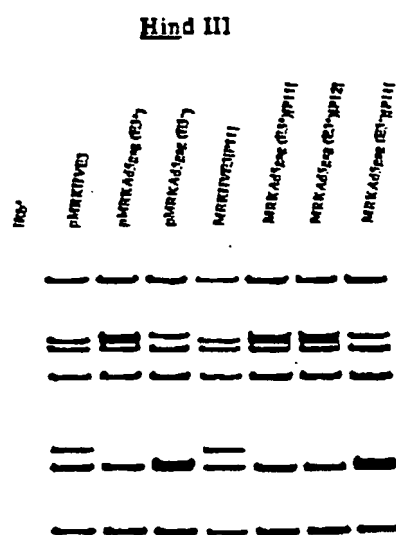


Figure 10: Viral DNA analysis of passage 11 and/or 12 of MRKHVE3, MRKAd5gag and MRKAd5gag(E3-).

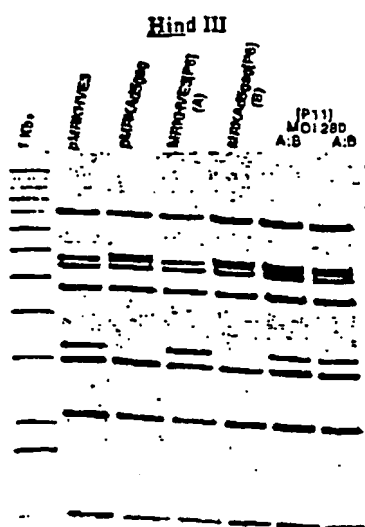


Figure 11: Viral DNA analysis (*Hind*III digestion) of passage 6 MRKHVE3 and MRKAd5gag used to initiate the viral competition study. Last two lanes are passage 11 analysis of duplicate passages of the competition study (each virus at MOI 280 vp).

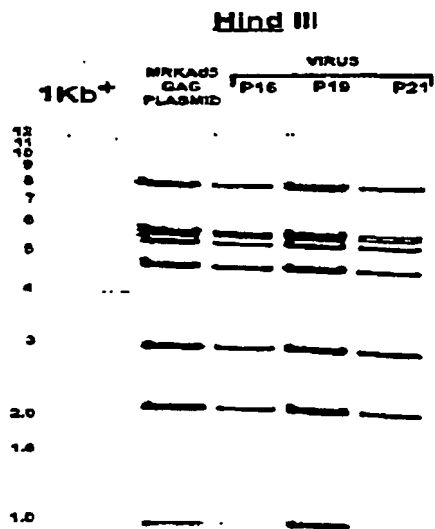
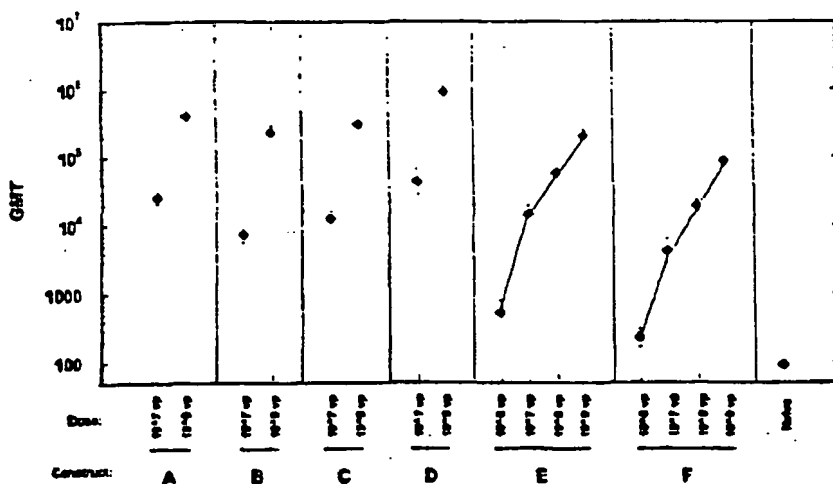


Figure 12: Viral DNA analysis by *Hind*III digestion on high passage numbers for MRKAd5gag in serum containing media with collections made at specified times. The first lane shows the 1 Kb DNA size marker. The other lanes represent pre-plasmid control (digested with *Pac*I and *Hind*III), and MRKAd5gag virus continually passaged to P16, P19 and P21 (serum containing media).

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 Figure 13. Serum anti-p24 Levels at 3 Wks post i.m. immunization of balb/c mice (n=10) with Varying Doses of Several Adgag constructs: (A) MRKAd5gag (through passage 5); (B) MRKAd5 E3' hCMV-FLgag-bGHpA; (C) MRKAd5 E3' hCMV-FLgag-SPA; (D) MRKAd5 E3' mCMV-FLgag-bGHpA; (E) research lot (293 cell-derived) of Ad5HIV-1gag; and (F) clinical lot (Ad5gagFN0001) of Ad5HIV-1gag. Reported are the geometric mean titers (GMT) for each cohort.



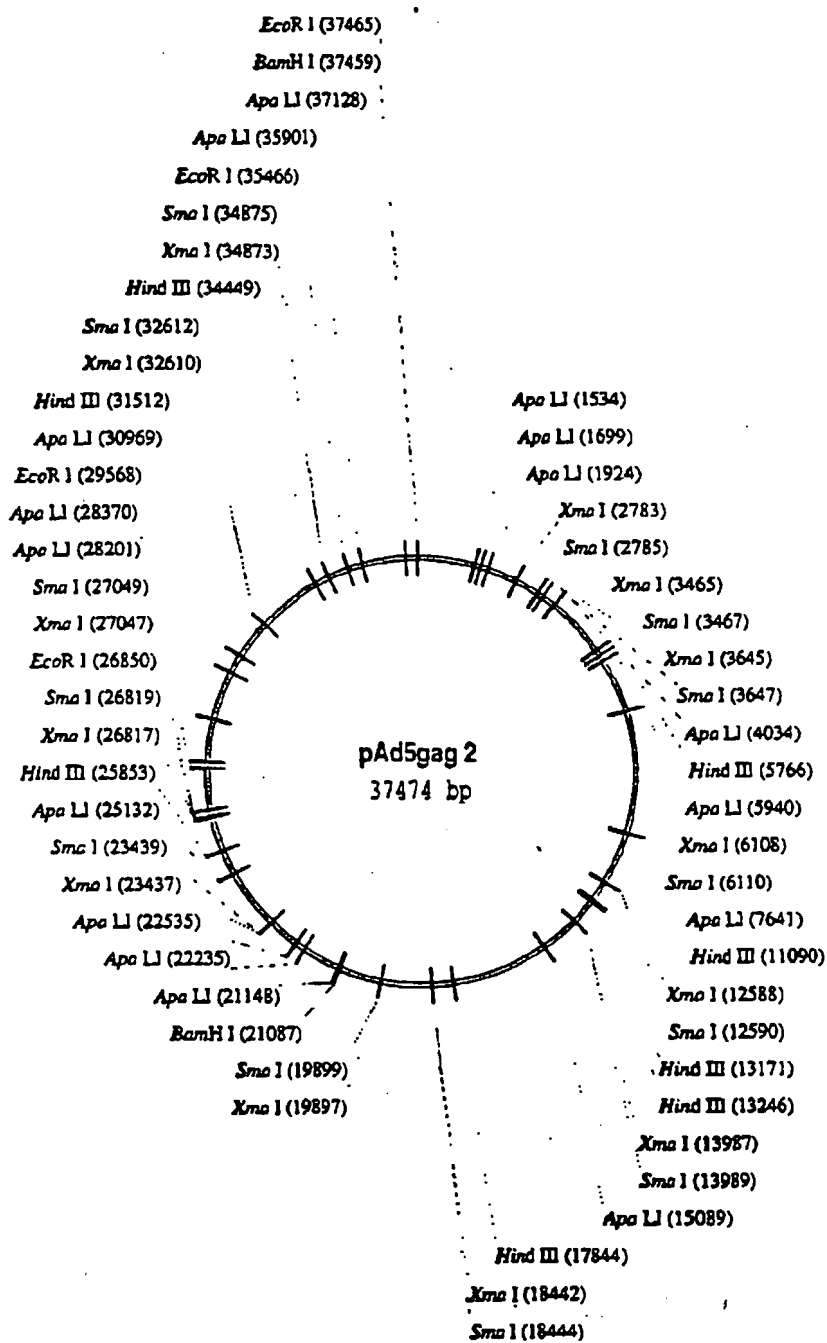


Figure 14

pNRKau194q MER6R2

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 GTGGTCCGCT AGAGGGGGC CTGGTCTTA CCGAGGACT TTACGATCT CTCTTCCCG AGAGCGGAC TCCACTAGCG GTACAGAGCA CCGACACGAC
 1801 AGGTGTCCAC CCGCCAGGAC CTGACATTA TTCTGATAC ATCTGATG CATTAGGTC GATAGGTCG CATTAGGTCG CATTAGGTCG CATTAGGTCG
 TCCAGCGTG GGGGTGCTG GACTGTGTT ACGATTTTG TCAATTTTG GATCTGTCG CATTAGGTCG CATTAGGTCG CATTAGGTCG CATTAGGTCG
 1901 TCAAGTGGAC AGCTGCGAT CTGTGATG TCACTGATG TCACTGATG TCACTGATG TCACTGATG TCACTGATG TCACTGATG TCACTGATG
 ACTGACCTG TCCGAGGTCG GACAGTGTG GACAGTGTG GACAGTGTG GACAGTGTG GACAGTGTG GACAGTGTG GACAGTGTG GACAGTGTG
 2001 CAGGAGCAGA TTGGTGTAT GACGATGAC CCGGATGAC CCGGATGAC CCGGATGAC CCGGATGAC CCGGATGAC CCGGATGAC CCGGATGAC
 GTCTCTGCT AACCGAGCTA CTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG
 2101 ACTGCGCCAC CTGCACTG GACATGATG AGCTGATG AGCTGATG AGCTGATG AGCTGATG AGCTGATG AGCTGATG AGCTGATG
 TGAAGGTCG GAGGTAGGAC CTGTGATG CTGTGATG CTGTGATG CTGTGATG CTGTGATG CTGTGATG CTGTGATG CTGTGATG
 2201 CCAAGAGGTC AGGACTGTA TCAAGAGAC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
 GTCTCTGCT AACCGAGCTA CTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG
 2301 GAGGAGATGA TCAAGAGAC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
 CTCTCTGCT AACCGAGCTA CTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG
 2401 TCAATGAGAG GGGGACTTC AGGAGAGTA AGGAGAGTA AGGAGAGTA AGGAGAGTA AGGAGAGTA AGGAGAGTA AGGAGAGTA AGGAGAGTA
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 2501 GAGGAGATGA TCAAGAGAC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
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 2601 AGGCTGTGCA ACTTCTCTA GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG
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 2701 AGGCTGTGCA ACTTCTCTA GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG
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 2801 CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
 TCCGAGGCT TCAAGAGAC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
 2901 TCCGAGGCT TCAAGAGAC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
 TCCGAGGCT TCAAGAGAC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
 3001 GAGGAGATGA TCAAGAGAC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
 CTCTCTGCT AACCGAGCTA CTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG GTGGTGTG
 3101 TCAAGAGAC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
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 3201 CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC
 TCCGAGGCT TCAAGAGAC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC CCGTGTGTC

Figure 15B

pHMKAd5gag MER602

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 CCAGCGAATC TCCGACCAAG ACTGACCACTA CTTCCTTATC GCTTCAAGCT GATCTCTGAG CAGCTCTATC ACCACAGTAT CAGTCTGGCT
 5001 TCCGCGCGCT GCGCTCTTGC GCGCAGCTTG CCGTCTTATC ATGCTCTCA CTCTCTTATC TCTGAGCTTT TTAGCGCTTA GAGCTTTCG GCTTCAATTA
 AGCGCGCGCA CCGGCAAGCG CCGCTGCAAC GCGAAGCTCC TCGCTCTCT CTCTCTCTCT ATCTCTCTCT ACTTCTCTCT CCGTCTCTCT
 5101 CCGATTCGCG GATATGAGCA TCTGCGCGC AGGCTCTCTA GATCTCTCT CATTCTAGCA GCTCTCTCT TCTGCGCTTA TATCTCTCT
 GCTTAGGCGC GCTCATCTCT AGCGCGCGCG TCGCGCGCT CTCTCTCTCT GATCTCTCT GATCTCTCT GATCTCTCT GATCTCTCT
 5201 TCCGCGCTAG TTTTCTATCC GTTCTCTTCC TCTCTCTCT ATGATCTCT GTCTCTCTCT GCTCTCTCT TCTGCGCTTA TATCTCTCT
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 5301 AGAGGCTCTGT CTTCTGAGCG TCTCTCTCT ATGATCTCT GTCTCTCTCT GATCTCTCT GATCTCTCT GATCTCTCT GATCTCTCT
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 5401 ATGCGGAGCG GTAGCGCTCT TTTCTCTCTA GCGCTCTCT AGCGCGCGCG TCTCTCTCT TCTCTCTCT TCTCTCTCT TCTCTCTCT
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Figure 15D

PHKAD5487 MERG2

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9801	TGAGAGCGTA	GTAGCGCTC	GTATGATAT	GTATGATAT	GTATGATAT	GTATGATAT	GTATGATAT	GTATGATAT	GTATGATAT	GTATGATAT
	ACTGTGCGT	CATTGCGAG	CTGATGTTT	GTATGATAT	GTATGATAT	GTATGATAT	GTATGATAT	GTATGATAT	GTATGATAT	GTATGATAT
9901	GGGCGAGCGT	AGGTGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG
	CCCGTCCCA	TCCGCGCGC	CCCGTCCCA	CCCGTCCCA	CCCGTCCCA	CCCGTCCCA	CCCGTCCCA	CCCGTCCCA	CCCGTCCCA	CCCGTCCCA
10001	GTGATGAGG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG
	CACGAGCTC	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG	GGGCGCGCG
10101	AATGCTTGC	GTCTAGACC	GTCTAGACC	GTCTAGACC	GTCTAGACC	GTCTAGACC	GTCTAGACC	GTCTAGACC	GTCTAGACC	GTCTAGACC
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10201	GGTGTGAGC	CCCGTATCG	CCCGTATCG	CCCGTATCG	CCCGTATCG	CCCGTATCG	CCCGTATCG	CCCGTATCG	CCCGTATCG	CCCGTATCG
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10301	TTGCGCTTC	TTGCGCTTC	TTGCGCTTC	TTGCGCTTC	TTGCGCTTC	TTGCGCTTC	TTGCGCTTC	TTGCGCTTC	TTGCGCTTC	TTGCGCTTC
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10401	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC
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10601	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC
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10701	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC
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10901	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC
	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG
11001	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC
	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG
11101	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC
	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG
11201	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC	GTGCGCTTC
	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG	CGAGCGAGG

Figure 15g

pMRKAd5gag MER6B2

11301	TGAAATTTGAT	AACATCTCTG	CAGAGATATG	TGATATAGGA	GTTGATTTTG	AGTTATCTTG	ATATATCTTG	GGCATATCAAC	TATTTCCATGC	TATAGGTACG	TTAGCTCTGT
11401	AGCTAAACTA	TTTGTAGGAC	GTCTGTATC	AGTACATCT	CTATATATAC	TTTATATATC	TTTATATATC	TTTATATATC	TTTATATATC	TTTATATATC	TTTATATATC
11501	CAGATTTTAC	GGCCGACAGA	TATATATATC	CTATATATC	CTATATATC	CTATATATC	CTATATATC	CTATATATC	CTATATATC	CTATATATC	CTATATATC
11601	GTTCATAATG	CGCCGATCT	ATATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC
11701	ACCTTATAGG	ACGACCTGCG	CTATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC	GGATATATC
11801	GGCTTCAATG	GGCTTCAATG	GGCTTCAATG	GGCTTCAATG	GGCTTCAATG	GGCTTCAATG	GGCTTCAATG	GGCTTCAATG	GGCTTCAATG	GGCTTCAATG	GGCTTCAATG
11901	CGATATATG	CGATATATG	CGATATATG	CGATATATG	CGATATATG	CGATATATG	CGATATATG	CGATATATG	CGATATATG	CGATATATG	CGATATATG
12001	CTCTCTCTCA	TTCTCTCTCA	TTCTCTCTCA	TTCTCTCTCA	TTCTCTCTCA	TTCTCTCTCA	TTCTCTCTCA	TTCTCTCTCA	TTCTCTCTCA	TTCTCTCTCA	TTCTCTCTCA
12101	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG
12201	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG
12301	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG
12401	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG
12501	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG
12601	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG
12701	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG
12801	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG	GGATATATG

Figure 15H

PMRKLd's seq MER6R2

12901 GTGATGATG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13001 ACCGCGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13101 TTTGCGCGCA GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13201 GTAGCGCGT GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13301 AGGAGCGTA GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13401 GAGTGTATG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13501 GAGGACGAT GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13601 GATGATGAT GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13701 TATGATGAT GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13801 GTGCGCGCG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 13901 ACAGGCGAC GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 14001 GAGGAGGAC GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 14101 ATATGATTA GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 14201 ACTGATGCG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 14301 GTATGATGCG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG
 14401 ATATGATGCG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG GTCTGACG

Figure 151

PHIRKAD500q MER6R2

14501	CTTACAGTGA TCTGAGGCT GTTACATTC CCGACATCT GTATGATGAC GTTATATAT GTAGCTTATA AGATGACAC GATCAGGCG GCGCTGATTC
14601	CGATCTACT AGACCTGCA CCAATGTAAG GCGCTTAAAG GCGCTTAAAG CCAATGTAAG GCGCTTAAAG CCAATGTAAG GCGCTTAAAG CCAATGTAAG
14701	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
14801	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
14901	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15001	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15101	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15201	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15301	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15401	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15501	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15601	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15701	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15801	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
15901	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC
16001	AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC AGATGACAC

Figure 15J

PMRKAU5nag MER682

16101	CCAGGTCATC	CGCGCGGAGA	TCATATGCTC	CGCGGAGGAG	GAGAGAGAGG	ATTATAGCTC	CTGAGAGCTA	ANGCGGCTCA	AAAGAGAAA	GAAGAGATAT
	GGTCCAGTAG	CGCGGCTCT	AGATACCGGG	GGCGTCTTTC	CTTATCTC	TAATATCTC	GAATATCTC	TTTCCGAGT	TTTCTTTT	CTTCTACT
16201	GATGATGAG	TTAGAGAG	AGTATGAG	CTTACAGCTA	CTTATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC
	CTACTACTTG	AGTATGAG	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC
16301	GCACGACCTT	AGTATGAG	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC
	CGTATGAG	TCAGAGAG	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC
16401	CGAGGCTCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC
	GGTATGAG	CGAGGCTCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC	GAATATCTC
16501	CTACAGAGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC
	GAATATCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
16601	AGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
16701	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
16801	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
16901	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
17001	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
17101	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
17201	ATATGAGAG	CTATATGCTC	AGTATGAG	CTATATGCTC	AGTATGAG	CTATATGCTC	AGTATGAG	CTATATGCTC	AGTATGAG	CTATATGCTC
	TTATATGCTC	AGTATGAG	CTATATGCTC	AGTATGAG	CTATATGCTC	AGTATGAG	CTATATGCTC	AGTATGAG	CTATATGCTC	AGTATGAG
17301	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
17401	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
17501	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG
	GGGCGGAGAG	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG	TCATATGCTC	AGTATGAG

Figure 15K

pmrkail5qbg HPER682

Eqn#	Seq#	Seq
17601	17601	TGCGACACAG CAGATGAGC GATTCGGCT TCAGTCTGTA CTCTTCTG AGCTTCTGCTT TCCACCTTT AGGACTATG AGGACTATG AGGACTATG
17701	17701	AGCGTGGTC GTTATGACTG CAGCGGCGA AGTTCAGCT GATTCAGCTT TCCACCTTT AGGACTATG AGGACTATG AGGACTATG
17801	17801	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
17901	17901	CACCTGGACC GTTATGACTG CAGCGGCGA AGTTCAGCT GATTCAGCTT TCCACCTTT AGGACTATG AGGACTATG AGGACTATG
18001	18001	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
18101	18101	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
18201	18201	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
18301	18301	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
18401	18401	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
18501	18501	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
18601	18601	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
18701	18701	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
18801	18801	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
18901	18901	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
19001	19001	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
19101	19101	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA
19201	19201	GTGACACCTG CAGACAGGC AGTGCAGAT AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA AGATTAACA

Figure 15L

pHRKAD5.dad MER6R2

19301 AGAAGTAAATG GGGGAGACAT CTATGCTCAA CAGGCTAAT TACATGCTT TTATGEM'AA TTTTATTTGT CTATGCTAAT ACACAGAGAC GGGTAAATAT
 19401 TCTTGATATC GGGTGTGTTA GATACGTGTT GTCCGZATTA ATGTAAAGAA AATGCTGTTT ANATAAGCA GATTACATAA TGTGTGCTG COCATTTATC
 19501 GGTGTGCTGG GGGGAGACAT TACGCTGCTG TATGCTGCTG TATGCTGCTG TATGCTGCTG TATGCTGCTG TATGCTGCTG TATGCTGCTG TATGCTGCTG
 19601 ATAGAGACAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 19701 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 19801 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 19901 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20001 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20101 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20201 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20301 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20401 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20501 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20601 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20701 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20801 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG
 20901 TATCTGCTGCTG CATGAGAGAG GGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG ATGTGCTGCTG

Figure 15M

УМКАДКА МЕРЗ

[illegible]

Figure 15N

pMRKΔJ5gaur MER682

22601	ATCTTGCCCT TCTTACACTG CTTCTTACAG GCGGCTTACG CTTCTTACCT ATTTCAATCA COTGCTCTCT ATTTATCAAA ATGCTTCTCT TAGAACCCGA AGGATCTGAC GATTAATTCG GCGGCTTACG GCGGCTTACG GCGGCTTACG GCGGCTTACG GCGGCTTACG
22701	GTAGACACTT AAGCTGCTT TCGATTTTAC GCGGCTTACG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CATCTGTGAA TTCTGAGCGA AGCTGAGCTG GCGGCTTACG GCGGCTTACG GCGGCTTACG GCGGCTTACG GCGGCTTACG
22801	CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GTCCATGCGG AGCTGCTTAC CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
22901	CATACGCGCG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GTATGCGCGC GCGCTGCGAG GTGACCAAT CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23001	CCATGCGCGT CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GTATGCGCGT CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23101	CCCATACCA CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GCGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23201	ACCATTTGTA CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG TCTTACAGAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23301	CTCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23401	CTCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23501	CTCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23601	CTCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23701	CTCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23801	CTCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
23901	CTCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
24001	CTCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG
24101	CTCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG GAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG CAGCTTACAG

Figure 15D

phrXad5 gag MER682

24201	CCTGACTCAA	CGAAGTACCA	AAATCTTTG	AGTATTTTG	AGCTGACG	ATGCTGCT	CAAGCTCT	CGAAGCTAA	ACAGCTGAA	ATGAAAGTCA
	GGAGCGATT	CTTCACGCT	TTTAGAAC	TTTATGTC	TTTATGTC	TTTATGTC	TTTATGTC	CTTGTGCT	TTTGTGCT	TACTTTTCACT
			NotI							
24301	CTCTGAGTG	TTGAGGAG	TTGAGGAG	CTATGCTAC	TAAATGAC	CTATGCTAC	CTATGCTAC	ACGCTGCT	ACGCTGCT	ACTTAACCTA
	GAGGCTCTAC	AGCTGCTAC	AGCTGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
24401	CCGCGGAGAG	TCATGAGAG	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC
	CCGCGGAGAG	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC	AGCTGCTAC
24501	TACCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	ATGCGGCTCA	ACGCTGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
			SpeI							
24601	TACCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	ATGCGGCTCA	ACGCTGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
			NotI							
24701	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
			NotI							
24801	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
			NotI							
24901	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
			NotI							
25001	GACATGATT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
25101	ACGCTGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	TCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
			NotI							
25201	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
			NotI							
25301	ACGCTGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	TCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
25401	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	CCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
25501	ACGCTGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	TCGCGGAGT	TCGCGGAG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
25601	TTTCTGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC
	AAAGAGGATG	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC	CTATGCTAC

Figure 15P

pHRKad⁺gag HIR682

25701	GGGCGCTTTC TTCCAGGAT GGCACCTAA AAGAACCTTC AATTTATTC GTATCTCAG GACAGAGAG AGTATCTGCTTCTCC	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
25801	TCGACGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
25901	ACCTGCTGCT CTGCTGCTTC TACTAGCTTC TGAGCTGCTC GATATGAGG GTTAAAGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26001	GGGAGGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26101	TCGACGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26201	ACCTGCTGCT CTGCTGCTTC TACTAGCTTC TGAGCTGCTC GATATGAGG GTTAAAGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26301	GGGAGGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26401	TCGACGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26501	ACCTGCTGCT CTGCTGCTTC TACTAGCTTC TGAGCTGCTC GATATGAGG GTTAAAGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26601	GGGAGGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26701	TCGACGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26801	GGGAGGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
26901	TCGACGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
27001	ACCTGCTGCT CTGCTGCTTC TACTAGCTTC TGAGCTGCTC GATATGAGG GTTAAAGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
27101	GGGAGGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT
27201	TCGACGAGGA GAGGAGGAG ATGATGAGG ACTGAGAGAG GTTAAAGAG GAGGAGGAG GAGGAGGAG	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT	GGTCTCAGAC AATATCTGGA CATTCTGGA GATATGATTTT

Figure 150

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27301 CCGTCCCGCC ACTATCCGGA TCAATTTAT CTAACTCTTG ACCTGTATTA GAGCTGTGCG GAGCTCTAGC ACTGATGTTT AGCTGAGAG GAGAGCAAC
 GGAAGGCGCG TGATAGGCGT AGTTANATTA GATTGAGAC TGTATTTAT CTCTAGCCGC CTGCTATGC TACTTACAA TACTCTCTC GATCTCTTT
 27401 TCGCCCTGAA AGACCTGTGC CACTGTCTC GGCACACTG GGCACACTG CTTTCTCTC GACTCTGCG GATTCTGTA CTTTCTGAT ATATCTGAT
 AGCGGACTT TGTGAGACCG GTGACACCG CGGTGTTCAC GAATTTGCG GATCTGCGG TCAAACTAT GAACTTTAC CCGCTCTAG TATAGCTCT
 27501 CCGCGCGCAC GCGTCTCGGC TTACCGCGCA GCGAGACTT GCGCTATGC TGAATCGGA TGAATCGGA CTTTCTGCG GATCTCTAG CCGCTCTAG
 GCGCGCGCG AATGCGCGT CCGCTCTGAA CCGCATGCG ACTAAGCGCT CAAATGCGT CAAATGCGT CAAATGCGT CAAATGCGT CAAATGCGT
 27601 CCGTCTGTTC TCACTGTGAT TTGCACACT TTGCACACT GATTACACT GATTACACT GATTACACT GATTACACT GATTACACT GATTACACT
 GCGACACGAG AGCTGACACTA AGCTGTGACA AGCTGTGACA AGCTGTGACA AGCTGTGACA AGCTGTGACA AGCTGTGACA AGCTGTGACA AGCTGTGACA
 27701 ATATCTGCGG GCTCTCTATC CCATCTCTGA ACCTCTCTGA ACCTCTCTGA ACCTCTCTGA ACCTCTCTGA ACCTCTCTGA ACCTCTCTGA ACCTCTCTGA
 TATATGACCC CGAGGATAGC GTATGAGCAT TTGCGGTGCG AGATGTGCG TCTTACCGCG CCGTCTCTCT GATCTCTCTG TACTCTCTG TACTCTCTG
 27801 GTATGATTTA CAACAGTTTC AACCGAGAG GATGAGTCT ACCAGAGAC GATGAGTCT ACCAGAGAC GATGAGTCT ACCAGAGAC GATGAGTCT ACCAGAGAC
 GACACTAAAT GTTGTGAAAG TTGCGTCTGC CTCACGAGA TCTCTCTCTG GATGAGTCT ACCAGAGAC GATGAGTCT ACCAGAGAC GATGAGTCT ACCAGAGAC
 27901 CCGGTAACCT ACCTGAGGCT CAGCGCGCG CAGCGCGCG CAGCGCGCG CAGCGCGCG CAGCGCGCG CAGCGCGCG CAGCGCGCG CAGCGCGCG
 GCGCTCTGCA TCTCTACGCA TCTCTACGCA TCTCTACGCA TCTCTACGCA TCTCTACGCA TCTCTACGCA TCTCTACGCA TCTCTACGCA TCTCTACGCA
 28001 AACAGAGCT GAGCTGTGAA AACCTTATG GTATTATGCG AATGAGTCTG AATGAGTCTG AATGAGTCTG AATGAGTCTG AATGAGTCTG AATGAGTCTG
 TTCTCTCTCA CTCGATCTT TTGCGATCTC CTATATCTCG GATGAGTCTG AATGAGTCTG AATGAGTCTG AATGAGTCTG AATGAGTCTG AATGAGTCTG
 28101 TCAAGTTTCT CTGAGATCGG GCTTGTGCT ATTCTGTGC TTGTGATCT CTTATCTCT ATACTACGC TTCTCTGCT AAGCTCTGC GCTCTCTC
 AGTCCAAAGA GATCTTACCC CCAACCCCAA TAAGAGAGAG AACACTAGA GAATATAGA TATGATTCG AGACACGGA TTCCGAGCG CCGAGGACAC
 28201 TCCACATTTG CATTTATTTT CAGCTTTTTC AACCTGCGG TCGCCACCA AGATGATTA GTACATATC CTAGCTTAC TCAGCTTAC GTCAGCTTAC
 ACCTGTAAAC GTATATACA GTGGAATAAT TTGCGACCC AGCGTCTGT TCTACTAATC CATGTATTA GATCCAAATG AGTGGAGAG CAGTCTGCT
 28301 GGTACCAGCC AATAGGTGGA TTATAGGAG CCACTCTGA AGTTACAT CTGAGCTGA AGTTACAT CTGAGCTGA AGTTACAT CTGAGCTGA AGTTACAT
 CCAATGTGCG TTCTCCACT AATATCTCT GGTGAGCAT TACAACTTAA GCTTCTGAT TACAACTTAA GCTTCTGAT TACAACTTAA GCTTCTGAT
 28401 ATGAAAGCT GCTTATTCG CACAAACA AATGTGCA GTATCTCT TTATCTCT TTATCTCT TTATCTCT TTATCTCT TTATCTCT
 TACTTTTCTA GGAATAGCG GTGTTTTTGT TTATCTCT TTATCTCT TTATCTCT TTATCTCT TTATCTCT TTATCTCT TTATCTCT TTATCTCT
 28501 CCAAGGTAAA AGTCAFAAA CTTTATGTA TACTTTTCTA TTATATGAA TGTGAGAT TACTATGTA TACTATGTA TACTATGTA TACTATGTA
 GGTGCGCATTT TCAATATTTT GAATATCAT ATGAAAGGT AATATCTTT ACAGCTGTA ATGATCAT ATGATCAT ATGATCAT ATGATCAT
 28601 CAATATGTTG TCGAAACAC TCGGCTTTC TGTGACTG CTATCTAT CTATCTAT CTATCTAT CTATCTAT CTATCTAT CTATCTAT
 GTTTTACAC ACCCTTTGTC ACCGTGAG AGGAGTGC GATACGATTA ATGTGAGAG GAAACGGA GATGATTA GATGATTA GATGATTA
 28701 GACGAGCTT TATTGAGGA AAGAAATGC CTTATTTTAC TATGTTACA AGTAAATTC ACTAAATTC ACTAAATTC ACTAAATTC ACTAAATTC
 CTGCTGCGAA ATAACTCTT TTCTTTTAC GATTTATAT ATTCAATCT TCGATTAAG TCTGATTA TCTGATTA TCTGATTA TCTGATTA
 28801 AATGTTAGC ATTAATATA GAATAGATT TAAACCGCC GGTCAATTC TCTGATTA TCTGATTA TCTGATTA TCTGATTA TCTGATTA
 TTTCATATG TAATATTAAT CTATCTTAA ATTTGCGCG CAGTAAAG ACGATTAAG ACGATTAAG ACGATTAAG ACGATTAAG

Figure 1SR

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28901 GGCCTACAC CTTGAGTCA GCTTCTCTG ATGTAGCAT CT ACTTGG CCAAGACTG TCCCTGGAT TCTTCCNGT CCACTACAG CCAACCACTC
 CCGATCTTG GAATCTCAAT CCGAAGATC TACAGTCTA CA TGAACC GATGCTGAC AGGCTGCTA ANCAAGCTCA GGTGATGTC GCTTCTCTG
 29001 TACAGGAT GACCAACCA ACCAAGCTG CCGCTGAC CCACTTACA TTATCCCA ATATCCGCA TATCTGCTC AGCTTCCG AATGATATA
 ATTCTCTA CTGCTCTG TCTTCTGCT CCGCTGATC GCTTCTCTG AGCTTCTCTG TATCTGCTC TCAAGGCTC TCAAGCTAT TCACTCTAT
 29101 CTGCTGAT TCTGCTCT CCAAGCTC GATAGCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GACCTGCTC ACCAAGCTC GATAGCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 29201 TATAGCTCA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 ATATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 29301 CATCTGCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 29401 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 29501 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 29601 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 29701 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 29801 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 29901 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 30001 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 30101 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 30201 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 30301 GCTTCTCT CCACTCTCTA TATCTCTG ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC
 GATCTCTA TCACTGCT ACACCTGAT ATATCTCTA TATCTCTG CATCTGCTC CTAAAGCTC ACCGCTGCTC ACCAAGCTC

Figure 155

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30401 AATTTCTCTG CAGTGTATAT CAGAGGACC TCTTGTGCT CTTCTCACT CTCTTATTCG AGCTTCCTCC TGGTGTCAA CTTCTCCAC ATTCTAAATG
 TTTAAAGACA GTTCATATTA GTCTGTGTG AGTAACGGA GTATGTATGA GATATATAGG TGGATATACG ACCGACGTTT GAAGAGGTG TTAGATTATC
 30501 GAATGTACGT TCTCTCTGT TCTGTGCAAT CCGTACCCAC TATCTTCATG TTTTGTATGA TGAAGTCCG TGAAGTCCG TGAAGTCCG TGAAGTCCG
 CTTCACATCA AGCAAGACA AGCAAGACA AGCAAGACA AGCAAGACA AGCAAGACA AGCAAGACA AGCAAGACA AGCAAGACA AGCAAGACA
 30601 GTATTCATAT GTACAGGAAA CCGTGTCTCC AGCTGTGCT TTTTCTCTG TTTTCTCTG TTTTCTCTG TTTTCTCTG TTTTCTCTG TTTTCTCTG
 CATAGGTATA CTGTGCTTT CCGTGTCTCC TTTTCTCTG TTTTCTCTG TTTTCTCTG TTTTCTCTG TTTTCTCTG TTTTCTCTG TTTTCTCTG
 30701 TCTTGTGCTC TATGTGATCC TCTTGTGATC TCTTGTGATC TCTTGTGATC TCTTGTGATC TCTTGTGATC TCTTGTGATC TCTTGTGATC TCTTGTGATC
 AGAAGGCGG ATAGCTTTGG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG
 30801 AATATGTAC CACTGTGAGC CCACTCTTCA AATATGTAC AATATGTAC AATATGTAC AATATGTAC AATATGTAC AATATGTAC AATATGTAC
 TTTTACATG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG
 30901 GGTGTGCTG CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG
 31001 GGTGTGCTG CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG
 31101 TACTACTGCT CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 ATTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG
 31201 AGAAGGCGG ATAGCTTTGG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG AGTACATGAG
 TTTTACATG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG GTACATGAG
 31301 GGTGTGCTG CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG CCGACGCGG
 31401 TACTACTGCT CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 ATTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG
 31501 GATTTGCTG CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 GTTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG
 31601 TCACTGCTG CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 GTTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG
 31701 TTAGTTTCTG CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 GTTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG
 31801 TGTAGGCTG CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 GTTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG
 31901 ATATGCTG CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 GTTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG
 32001 GATTTGCTG CACTGTGAG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG TGTGTGCTG
 GTTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG GTATGCTG

Figure 15T

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32101 TAACTATGTC AGTCAGATTT ACTTAAGCGG AGCAAAAGCT AAKK'YKTA CACTAACCT TACTACTAAC GGTACACAGB ANACAGBGA CACNACTCA
 ATTGTAAAGG TCGATTGAAA TGATTTTTCG TCTGTTTTCG TTTTACACT GTGATTTTGG CCAATGTGTC TTGTGCTGCT TTGTGCTGCT GTTGTGAGT
 32201 AGTGCATACT CTATGTCATT TTCAATGAGC TTCTCTGCTG AGCAATACAT TAATGAAATA TTCTCTGCTG TTCTCTGCTG TTCTCTGCTG ATTGCCAN
 TCACTATATG GATACAGTAA AGGTACCTCG ATCAAGACCG TTCTCTGCTG TTCTCTGCTG TTCTCTGCTG TTCTCTGCTG TTCTCTGCTG TTCTCTGCTG
 32301 AATAAGAAAT GCTTTGCTGTT ATGTTTCMAC GCTTTGCTGTT CACAAATGAG CACAAATGAG CACAAATGAG CACAAATGAG CACAAATGAG CACAAATGAG
 TTAATTTCTTA GCAACACAAA TACAAAGTGG TACAAAGTGG TACAAAGTGG TACAAAGTGG TACAAAGTGG TACAAAGTGG TACAAAGTGG TACAAAGTGG
 32401 GCTTATACAG ATCAAGCTGAC CTTAAATGAA GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 CCAATATATG TATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 32501 GCTGCTCTTA AAGAGCATCA TATCATGCTG TATCATGCTG TATCATGCTG TATCATGCTG TATCATGCTG TATCATGCTG TATCATGCTG TATCATGCTG
 GAGCGGAAAT TTTTGTGAGT ATAGTACCTG ATAGTACCTG ATAGTACCTG ATAGTACCTG ATAGTACCTG ATAGTACCTG ATAGTACCTG ATAGTACCTG
 32601 ATAAAGTCTC GAGGAGCTG ACTTATGCTG ACTTATGCTG ACTTATGCTG ACTTATGCTG ACTTATGCTG ACTTATGCTG ACTTATGCTG ACTTATGCTG
 TATTTTACGG GCGGCTGCGG TGAATTCAG TGAATTCAG TGAATTCAG TGAATTCAG TGAATTCAG TGAATTCAG TGAATTCAG TGAATTCAG TGAATTCAG
 32701 AAGTCCAGCC CTACATGCGG GTAGATGCTG ATGCTGCTG CAGATATGAG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 TTGAGTGGCG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 32801 CCTGACAGAA TACAGATGCG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 32901 TCACTTAAT TACAGATGCG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 AGTGAATTTA GTGATGCTG TACAGATGCG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 33001 AACCCAGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 TTGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 33101 CACGAGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 GTGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 33201 AGGGAAGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 TCGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 33301 GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 33401 AAGAGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 TCGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 33501 GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG
 GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG GATGATGCTG

Figure 15U

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33601 CTGAGACAAA ACCAGGTGCG GCGGTACAAA ACAGATCTTC GTCCTCTGTC TTTGCTGTGA GATGCTCTCG TGTAGTAGTT GTATATATAT CACTCTCTTA
 GACTTCCTTT TGTGTCAGGC CGCGATCTTT TGTCTAGACG CAGAGCTGTC CAGAGCTGTC AGTGGGAT ACATCATCAA CAGCATATAG GTTAGAGATT
 33701 AAGCATCCAG GCGCGCCCTG GCTTCGGATT CTATGTAAAC TCTCTATGTC TCTCTATGTC CCGCTGCTCC TATATACATC CACCACCGCA GANTAGGCA CACCCAGCC/
 TCTGTAGTTC CCGCGCCGAC CGAGCGCCAA GATACATATG AGTAGTAGTC CCGCTGCTCC AGTATGTATG ACTATGTATG GTTATGTCTT GTGGCTCTGJ
 33801 ACCTACACAT TGTCTCTGCG AGTACACACAG CGGAGTATGCT GTAGAGTCTG GTAGAGTCTG GTAGAGTCTG GTAGAGTCTG GTAGAGTCTG GTAGAGTCTG
 TGTAGTCTGA AGCAGAGAGC TGTAGTCTGCT GCTCTCTGTC CTTCTCTGTC CTTCTCTGTC CTTCTCTGTC CTTCTCTGTC CTTCTCTGTC CTTCTCTGTC
 33901 ATGAGAGATCT ATTATGTGAA GCGGTGCTCC TCGGTGCTCC TGTCTGCTCC TGTCTGCTCC TGTCTGCTCC TGTCTGCTCC TGTCTGCTCC TGTCTGCTCC
 TACTCTTAGA TATTTCACTT GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC
 34001 TCCAAAGGC AAGCGCCCTG CAGGTCCAG TCGAGTAAAC GGTAAAGCC TTAAGGTGTA ATCTGCTCTA TAAACATTC ACCACCTTCA ACCATGCCCC
 AGGTCTCTCC TTTGCGCGGA GTGCGGCTTC ACCTGCTATT CCGATTTGCG AAGTCCCACT TAGAGAGGAT ATTGTATAGG TCGTGTAAAT TGTAGCGGCT
 34101 ANTAATCTC ATCTGCTCC CTTCTGCTAA TATCTCTAAG CTAATCTGTA ATATTAGTC GCGGTGCTCC TAAATCTGTC TCCAGAGGCG CCTGCGCTTT
 TTATTAGAG TAGAGCGGTC GAGAGGTTAT ATAGAGTCTC GTTTAGGCT TATAATTCAG GCGGTGCTCC TTTTAGAGCG AGGTCTGCGC GAGGTGCGA
 34201 CAGCTCTCAG CAGCGAATCA TGAATGCAAA AATTCAGGTT CCTGCTCAG CTTGCTCAG CTTGCTCAG CTTGCTCAG CTTGCTCAG CTTGCTCAG
 GTGCGAGTTC GTGCTCTGCT ACTAGCTTTT TTAAGTCCAA GGTAGTCTGTA GATATATCT AATTTTCTCC GTTGTATGCT TTTTATGCT GCTAGGCTAT
 34301 GTTCTCTCTG CAGGCTCAG TGAACATAT GTTCTGCTC GAGTCTGCTC GAGTCTGCTC GAGTCTGCTC GAGTCTGCTC GAGTCTGCTC GAGTCTGCTC
 CAGGCTCAG GAGTCTGCTC ACTGCTATTA GAGTCTGCTC GAGTCTGCTC GAGTCTGCTC GAGTCTGCTC GAGTCTGCTC GAGTCTGCTC GAGTCTGCTC
 34401 TATGAGAGC ATACTGCTG CTATGCTAC CAGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC
 ATACTGCTG TATGAGCTTC GATAGCTATG GTGCTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC
 34501 GCGAGAGCT GCGGTGCTCC GATAGCTATG GTGCTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC
 CCGTCTGCG GCGGTGCTCC TCTGCTGCT AGATCTGCTC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC
 34601 TCTCAACAT GTCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT
 AGATCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT
 34701 ATAGAGCTTA GAGGTGCTAC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC
 TATGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT
 34801 TCAATATGTA AGATGCTGTA AACATCTAG GTTGTATGCT GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC GCGGTGCTCC
 AGATGCTAT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT
 34901 AGATGCTAT AGATGCTAT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT
 TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT
 35001 TCTGCTGCT GAGATGCTA CAGGTCTTC CAGGTCTTC CAGGTCTTC CAGGTCTTC CAGGTCTTC CAGGTCTTC CAGGTCTTC CAGGTCTTC CAGGTCTTC
 AGATGCTAT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT TCTGCTGCT
 35101 GCGGTGCTCC CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA
 CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA
 35201 CCGGTGCTCC CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA
 CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA CAGGTGCTA

Figure 15V

PMRKA05seq HERG82

37001 CACACCGGA TAAATCCCGG CCACATATCA GAACCTTAAA AGTGTCTATC ATTGTAAAC GTTCTTCGGG GCGAAACAC TCACGATCT TACTTCTTT
 GTTGTGCGCT ATTATCGCGC GGTATCGCGC GTTGAATTT TACAGCTAG TACCTTTTG CAGACGCC CCGTTTGG AGTCTCTCA ATGCTGACA
 37101 GAGATCCAGT TCGATGTAC CCACTCGTC ACCTACCTCA TCTTATAT TTTTACTTT CACTGCTTT TGTGCTGAG CAAACACAG AGCGCAAAAT
 CTCTAGGTCA AGCTACATG GGTGACAGC TGGGTGACT AGAATCTTGA GAAATGAAA GTGTCTGCA AGCCCACTC GTTTTGTCC TTGCTTTTAA
 37201 GCGCCAAAA AGGGAATAG GCGACACAG ANATGTGAA TACTATAT TTTCTTTT CATATATT GAGCATTTA TCAGTATT TCTCTCATCA
 CCGCTTTTT TCGCTTATC CCGCTGACC TTTCACATC ATGACTATCA GAGGAAAA GTTATATTA CTTCGTAAAT AGTCCCAATA ACAGAGTAT
 37301 GCGGATACAT ATTGAAATG ATTAGAAA ATAAACAAAT AGGATTTT GAGATTTT CCGGAAATG GCGACCTGAC GTCTAAGAAA CCAATTATT
 CCGCTATGTA TAACTTTACA TAAATCTTT TATTGTTTA TCCCCACGC CCGTGTAAAG GCGCTTTTCA CCGTGGACTG CAGTCTCTT CCGTAAATA
 BamHI
 37401 CATGACATTA ACCTATAAA ATAGCGTAT CACTAGCGC TTCTCTTTC AGAATTTGA TTGATTTCT TAAT (SEQ ID NO: 27)
 GTACTGTAT TGGATATTT TATCCGATA GGTCTCGCG TATCCACT AGCTTAAA ATTA (SEQ ID NO: 28)

Figure 15X

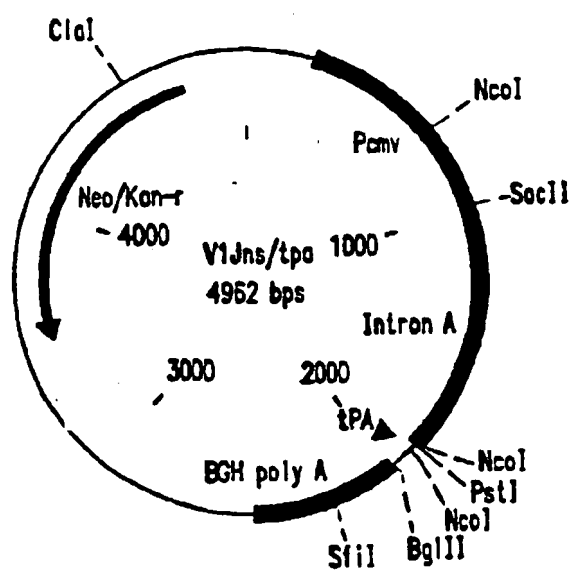
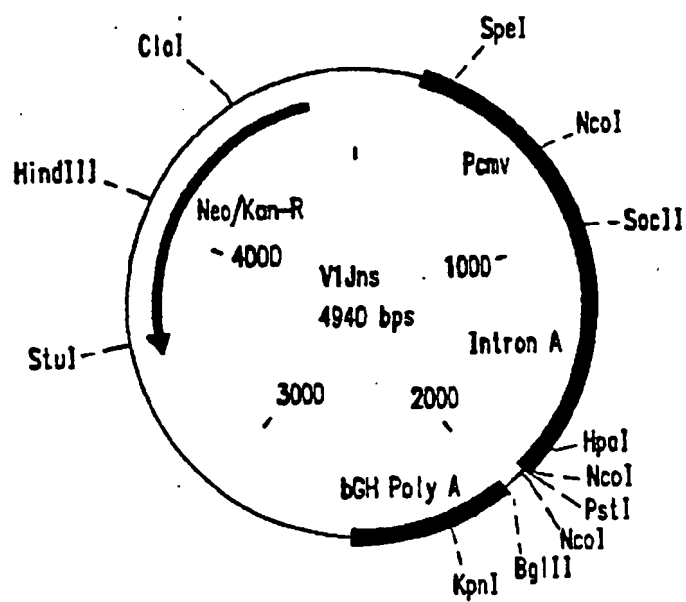


FIGURE 16

AGATCTACCATGGCCCCCATCTCCCCATTGAGACTGTCCCTGTGAAGCTGAAGCCTGGCATGGATGGCCCCAAGGTGAA
 Bg/II MetAlaProIleSerProIleGluThrValProValLysLeuLysProGlyMetAspGlyProLysValLy
 1 10 20
 GCAGTGGCCCCGACTGAGGAGAAGATCAAGCCCCGTGGAAATCTGCACTGAGATGGAGAAGGAGGGCAAAATCTCCA
 sGlnTrpProLeuThrGluGluLysIleLysAlaLeuValGluIleCysThrGluMetGluLysGluGlyLysIleSerL
 30 40 50
 AGATTGGCCCCGAGAAGCCCTACACACCCCTGTGTTTGCCATCAAGAAGAAGGACTCCACCAAGTGGAGGAAGCTGGTG
 ysIleGlyProGluAsnProTyrAsnThrProValPheAlaIleLysLysLysAspSerThrLysTrpArgLysLeuVal
 60 70
 GACTTCAGGAGCTGAACAAGAGGACCCAGGACTTCTGGGAGGTGCAGCTGGGCATCCCCACCCCGCTGGCCTGAAGAA
 AspPheArgGluLeuAsnLysArgThrGlnAspPheTrpGluValGlnLeuGlyIleProHisProAlaGlyLeuLysLy
 80 90 100
 GAAGAAGTCTGTGACTGTGCTGGCTGTGGGGATGCCACTTCTGTGCCCCCTGGATGAGGACTTCAGGAAGTACACTG
 slsLysSerValThrValLeuAlaValGlyAspAlaTyrPheSerValProLeuAspGluAspPheArgLysTyrThrA
 110 120 130
 CCTTCACCATCCCCCTCCATCAACAATGAGACCCCTGGCATCAGGTACCAGTACAATGTGCTGCCCCAGGGCTGGAAGGGC
 loPheTnrIleProSerIleAsnAsnGluThrProGlyIleArgTyrGlnTyrAsnValLeuProGlnGlyTrpLysGly
 140 150
 TCCCCTGCCATCTTCCAGTCTCTCCATGACCAAGATCCTGGAGCCCTTCAGGAAGCAGAACCCTGACATTGTGATCTACCA
 SerProAlaIlePheGlnSerSerMetThrLysIleLeuGluProPheArgLysGlnAsnProAspIleValIleTyrGl
 160 170 180
 GTACATGGCTGCCCTGTATGTGGCTCTGACCTGGAGATTGGGCAGCACAGGACCAAGATTGAGGAGCTGAGGCAGCAAC
 nTyrMetAlaAlaLeuTyrValGlySerAspLeuGluIleGlyGlnHisArgThrLysIleGluGluLeuArgGlnHisL
 190 200 210
 TGCTGAGGTGGGCGCTGACCACCCCTGACAAGAAGCACCAGAAGGAGCCCCCTTCTGTGGATGGGCTATGAGCTGCAC
 euLeuArgTrpGlyLeuThrThrProAspLysLysHisGlnLysGluProProPheLeuTrpMetGlyTyrGluLeuHis
 220 230
 CCGACAAGTGGACTGTGCAGCCCATTTGCTGCTGAGAAGGACTCCTGGACTGTGAATGACATCCAGAAGCTGGTGGG
 ProAspLysTrpThrValGlnProIleValLeuProGluLysAspSerTrpThrValAsnAspIleGlnLysLeuValGl
 240 250 260
 CAAGCTGAAGTGGGCTCCCAAATCTACCCCTGGCATCAAGGTGAGGCAGCTGTGCAAGCTGCTGAGGGGCACCAAGGCC
 yLysLeuAsnTrpAlaSerGlnIleTyrProGlyIleLysValArgGlnLeuCysLysLeuLeuArgGlyThrLysAlaL
 270 280 290

FIGURE 17A

TGA CTGAGG TGATCCCCCTGACTGAGGAGGCTGAGCTGGAGCTGGCTGAGAACAGGCAGATCCTGAAGGAGCCTGTGCAT
 EuThrGluVolIleProLeuThrGluGluAlaGluLeuGluLeuAlaGluAsnArgGluIleLeuLysGluProVolHis
 300 310

GGGCTG TACTATGACCCCTCCAAGGACCTGATTGCTGAGATCCAGAAGCAGGGCCAGGGCCAGTGGACCTACCAATCTA
 GlyVolTyrTyrAspProSerLysAspLeuIleAlaGluIleGlnLysGlnGlyGlnGlyGlnTrpThrTyrGlnIleTy
 320 330 340

CCAGGAGCCCTTCAAGAACCTGAAGACTGGCAAGTATGCCAGGATGAGGGGGCCACACCAATGATGTGAAGCAGCTGA
 rGlnGluProPheLysAsnLeuLysThrGlyLysTyrAlaArgMetArgGlyAlaHisThrAsnAspVolLysGlnLeuT
 350 360 370

CTGAGGCTGTGCAGAGATCACCCTGAGTCCATTGTGATCTGGGCAAGACCCCAAGTTCAGCTGCCATCCAGAAG
 hrGluAlaVolGlnLysIleThrThrGluSerIleVolIleTrpGlyLysThrProLysPheLysLeuProIleGlnLys
 380 390

GAGACCTGGGAGACCTGGTGGACTGAGTACTGGCAGGCCACCTGGATCCCTGAGTGGGAGTTTGTGAACACCCCCCCT
 GluThrTrpGluThrTrpTrpThrGluTyrTrpGlnAlaThrTrpIleProGluTrpGluPheVolAsnThrProProLe
 400 410 420

GGTGAAGCTGTGGTACCAGCTGGAGAAGGAGCCATTGTGGGGCTGAGACCTTCTATGTGGCTGGGGCTGCCAACAGGG
 uVolLysLeuTrpTyrGlnLeuGluLysGluProIleVolGlyAlaGluThrPheTyrVolAlaGlyAlaAlaAsnArgG
 430 440 450

AGACCAAGCTGGGCAAGGCTGGCTATGTGACCAACAGGGCAGGCAGAGGTTGGTGACCCTGACTGACACCACCAACCG
 luThrLysLeuGlyLysAlaGlyTyrVolThrAsnArgGlyArgGlnLysVolVolThrLeuThrAspThrThrAsnGln
 460 470

AAGACTGCCCTCCAGGCCATCTACCTGGCCCTCCAGGACTCTGGCCTGGAGGTGAACATTGTGACTGCCCTCCAGTATGC
 LysThrAlaLeuGlnAlaIleTyrLeuAlaLeuGlnAspSerGlyLeuGluVolAsnIleVolThrAlaSerGlnTyrAl
 480 490 500

CCTGGGCATCATCCAGGCCAGCCTGATCAGTCTGAGCTGAGCTGGTGAACCAGATCATTGAGCAGCTGATCAAGAAGG
 aLeuGlyIleIleGlnAlaGlnProAspGlnSerGluSerGluLeuVolAsnGlnIleIleGluGlnLeuIleLysLysG
 510 520 530

AGAAGGTGTACCTGGCTGGCTGGCTGCCACAAGGCCATTGGGGCAATGAGCAGGTGGACAAGCTGGTGTCTGCTGGC
 luLysVolTyrLeuAlaTrpVolProAlaHisLysGlyIleGlyGlyAsnGluGlnVolAspLysLeuVolSerAlaGly
 540 550

ATCAGGAAGGTGCTGTTCCTGGATGGCATTGACAAGGCCAGGATGAGCATGAGAAGTACCACTCCAAGTGGAGGGCTAT
 IleArgLysValLeuPheLeuAspGlyIleAspLysAlaGlnAspGluHisGluLysTyrHisSerAsnTrpArgAlaMe
 560 570 580

FIGURE 17B

GGCCTCTGACTTCAACCTGCCCTGTGGTGGCTAAGGAGATTGTGGCTCCTGTGACAAGTCCAGCTGAAGGGGAGG
 tAlaSerAspPheAsnLeuProProVolVolAlaLysGluIleVolAlaSerCysAspLysCysGlnLeuLysGlyGluA
 590 600 610

CCATGCATGGGCAGGTGGACTGCTCCCTGGCATCTGGCAGCTGGCCTGCACCCACCTGGAGGGCAAGGTGATCCTGCTG
 lAlaMetHisGlyGlnVolAspCysSerProGlyIleTrpGlnLeuAlaCysThrHisLeuGluGlyLysVolIleLeuVol
 620 630

GCTGTGCAATGTGGCTCCGGCTACATTGAGGCTGAGGTGATCCCTGCTGAGACAGGCCAGGAGACTGCCTACTTCTGCT
 AlaVolHisVolAlaSerGlyTyrIleGluAlaGluVolIleProAlaGluThrGlyGlnGluThrAlaTyrPheLeuLe
 640 650 660

GAAGCTGGCTGGCAGGTGGCCTGTGAAGACCATCCACACTGCCAATGGCTCCAACCTCACTGGGGCCACAGTGAGGGCTG
 uLysLeuAlaGlyArgTrpProVolLysThrIleHisThrAlaAsnGlySerAsnPheThrGlyAlaThrVolArgAlaA
 670 680 690

CCTGCTGGTGGCTGGCATCAAGCAGGAGTGTGGCACTCCCTACAACCCCACTCCAGGGGTGGTGGCTCCATGAAC
 lAlaCysTrpTrpAlaGlyIleLysGlnGluPheGlyIleProTyrAsnProGlnSerGlnGlyVolVolAlaSerMetAsn
 700 710

AAGGAGCTGAAGAAGATCATTTGGCAGGTGAGGGACCAGCTGAGCACCTGAAGACAGCTGTGCAGATGGCTGTGTTTAT
 LysGluLeuLysLysIleIleGlyGlnVolArgAspGlnAlaGluHisLeuLysThrAlaVolGlnMetAlaVolPheIle
 720 730 740

CCACAACCTCAAGAGGAAGGGGGCATCGGGGCTACTCCGCTGGGAGAGGATTGTGGACATCATGCCACAGACATCC
 eHisAsnPheLysArgLysGlyGlyIleGlyGlyTyrSerAlaGlyGluArgIleVolAspIleIleAlaThrAspIleG
 750 760 770

AGACCAAGGAGCTCCAGAAGCAGATCACCAAGATCCAGAAGTTCAGGGTGTACTACAGGACTCCAGGAACCCCTGTGG
 lThrLysGluLeuGlnLysGlnIleThrLysIleGlnAsnPheArgVolTyrTyrArgAspSerArgAsnProLeuTrp
 780 790

AAGGGCCCTGCCAAGCTGCTGTGGAAGGGGAGGGGGCTGTGGTGATCCAGGACAACCTCTGACATCAAGGTGGTGGCCAG
 LysGlyProAlaLysLeuLeuTrpLysGlyGluGlyAlaVolVolIleGlnAspAsnSerAspIleLysVolVolProAr
 800 810 820

GAGGAAGGCCAAGATCATCAGGGACTATGGCAAGCAGATGGCTGGGATGACTGTGTGGCTCCAGGCAGGATGAGGACT
 gArgLysAlaLysIleIleArgAspTyrGlyLysGlnMetAlaGlyAspAspCysValAlaSerArgGlnAspGluAspx
 830 840 850

AAAGCCCGGCAGATCT (SEQ ID NO: 3)
 Xx BgllI (SEQ ID NO: 4)

FIGURE 17C

WT	- ATG GGT GGC AAG TGG TCA AAA CGT AGT GTG CCT GGA TGG TCT	-42
OPT	- ATG GGC GGC AAG TGG TCC AAG AGG TCC GTG CCC GGC TGG TCC M G G K W S K R S V P G W S	-14
WT	- ACT GTA AGG GAA AGA ATG AGA CGA GCT GAG CCA GCA GCA GAT	-84
OPT	- ACC GTG AGG GAG AGG ATG AGG AGG GCC GAG CCC GCC GCC GAC T V R E R M R R A E P A A D	-28
WT	- AGG GTG AGA CGA ACT GAG CCA GCA GCA GTA GGG GTG GGA GCA	-126
OPT	- AGG GTG AGG AGG ACC GAG CCC GCC GCC GTG GGC GTG GGC GCC R V R R T E P A A V G V G A	-42
WT	- GTA TCT CGA GAC CTG GAA AAA CAT GGA GCA ATC ACA AGT AGC	-168
OPT	- GTG TCC AGG GAC CTG GAG AAG CAC GGC GCC ATC ACC TCC TCC V S R D L E K H G A I T S S	-56
WT	- AAT ACA GCA GCT ACC AAT GCT GAT TGT GCC TGG CTA GAA GCA	-210
OPT	- AAC ACC GCC GCC ACC AAC GCC GAC TGC GCC TGG CTG GAG GCC N T A A T N A D C A W L E A	-70
WT	- CAA GAG GAT GAG GAA GTG GGT TTT CCA GTC AGA CCT CAG GTA	-252
OPT	- CAG GAG GAC GAG GAG GTG GGC TTC CCC GTG AGG CCC CAG GTG Q E D E E V G F P V R P Q V	-84
WT	- CCT TTA AGA CCA ATG ACT TAC AAG GGA GCT GTA GAT CTT AGC	-294
OPT	- CCC CTG AGG CCC ATG ACC TAC AAG GGC GCC GTG GAC CTG TCC P L R P M T Y K G A V D L S	-98
WT	- CAC TTT TTA AAA GAA AAG GGG GGA CTG GAA GGG CTA ATT CAC	-336
OPT	- CAC TTC CTG AAG GAG AAG GGC GGC CTG GAG GGC CTG ATC CAC H F L K E K G G L E G L I H	-112
WT	- TCA CAG AAA AGA CAA GAT ATC CTT GAT CTG TGG GTC TAC CAC	-378
OPT	- TCC CAG AAG AGG CAG GAC ATC CTG GAC CTG TGG GTG TAC CAC S Q K R Q D I L D L W V Y H	-126
WT	- ACA CAA GGC TAC TTC CCT GAT TGG CAG AAC TAC ACA CCA GGG	-420
OPT	- ACC CAG GGC TAC TTC CCC GAC TGG CAG AAC TAC ACC CCC GGC T Q G Y F P D W D N Y T P G	-140

FIGURE 19A

WT	- CCA GGA ATC AGA TTT CCA TTG ACC TTT GGA TGG TGC TTC AAG	-462
OPT	- CCC GGC ATC AGG TTC CCC CTG ACC TTC GGC TGG TGC TTC AAG	
	P G I R F P L T F G W C F K	-154
WT	- CTA GTA CCA GTT GAG CCA GAA AAG GTA GAA GAG GCC AAT GAA	-504
OPT	- CTG GTG CCC GTG GAG CCC GAG AAG GTG GAG GAG GCC AAC GAG	
	L V P V E P E K V E E A N E	-168
WT	- GGA GAG AAC AAC TGC TTG TTA CAC CCT ATG AGC CAG CAT GGG	-546
OPT	- GGC GAG AAC AAC TGC CTG CTG CAC CCC ATG TCC CAG CAC GGC	
	G E N N C L L H P M S Q H G	-182
WT	- ATA GAG GAC CCG GAG AAG GAA GTG TTA GAG TGG AGG TTT GAC	-588
OPT	- ATC GAG GAC CCC GAG AAG GAG GTG CTG GAG TGG AGG TTC GAC	
	I E D P E K E V L E W R F D	-196
WT	- AGC AAG CTA GCA TTT CAT CAC GTG GCC CGA GAG CTG CAT CCG	-630
OPT	- TCC AAG CTG GCC TTC CAC CAC GTG GCC AGG GAG CTG CAC CCC	
	S K L A F H H V A R E L H P	-210
WT	- GAG TAC TAC AAG GAC TGC TGA (SEQ ID NO:30)	-651
OPT	- GAG TAC TAC AAG GAC TGC TAA (contained within SEQ ID NO:9)	
	E Y Y K D C (SEQ ID NO:10)	-216

FIGURE 19B

VIJns/nef *PstI* *BglII*
 CATGGGTCCTTTCTGAGTACCGTCTCTTGAATCTGCCACC ATG GGC GGC AAG TGG TCC MAG AGG TCC GTG CCC
 M G G K W S K R S V P
 CAC CCC GAG TAC TAC ANG GAC TGC TAA AGCCCGGACAGATCTGCTGTGCTTCTAGTTGCCAGC (SEQ ID NO: 38)
 H P E Y Y K D C * (contained within SEQ ID NO: 10) *SrfI* *BglII*

VIJns/nef(G2A, LLAA)
PstI *BglII*
 CATGGGTCCTTTCTGAGTACCGTCTCTTGAATCTGCCACC ATG GGC GGC ANG TGG TCC AAG AGG TCC GTG CCC
 M A G K W S K R S V P
 CAC CCC GAG TAC TAC ANG GAC TGC TAA AGCCCGGACAGATCTGCTGTGCTTCTAGTTGCCAGC (SEQ ID NO: 39)
 H P E Y Y K D C * (contained within SEQ ID NO: 14) *SrfI* *BglII*

VIJns/tpanef & VIJns/tpanef(LLAA)
PstI
 CATGGGTCCTTTCTGAGTACCGTCTCTTATATCTAGATCACC ATG GAT GCA ATG MAG AGA GGG CTC TGC TGT GTG
 M D A M K R G L C V
 CTG CTG CTG TGT GGA GCA GTC TTC GTT TCG CCC AGC GAG ATC TCC TCC MAG AGG TCC GTG CCC
 L L L C G A V F V S P S E I S S K R S V P
 CAC CCC GAG TAC TAC ANG GAC TGC TAA AGCCCGGACAGATCTGCTGTGCTTCTAGTTGCCAGC (SEQ ID NO: 40)
 H P E Y Y K D C * (contained within SEQ ID NO: 16) *SrfI* *BglII*

FIGURE 20

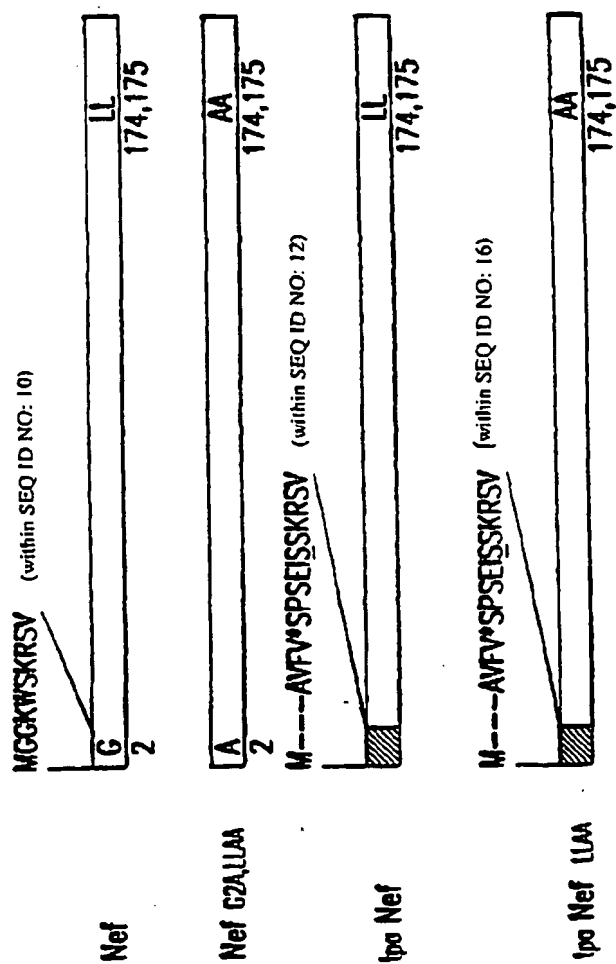


FIGURE 21

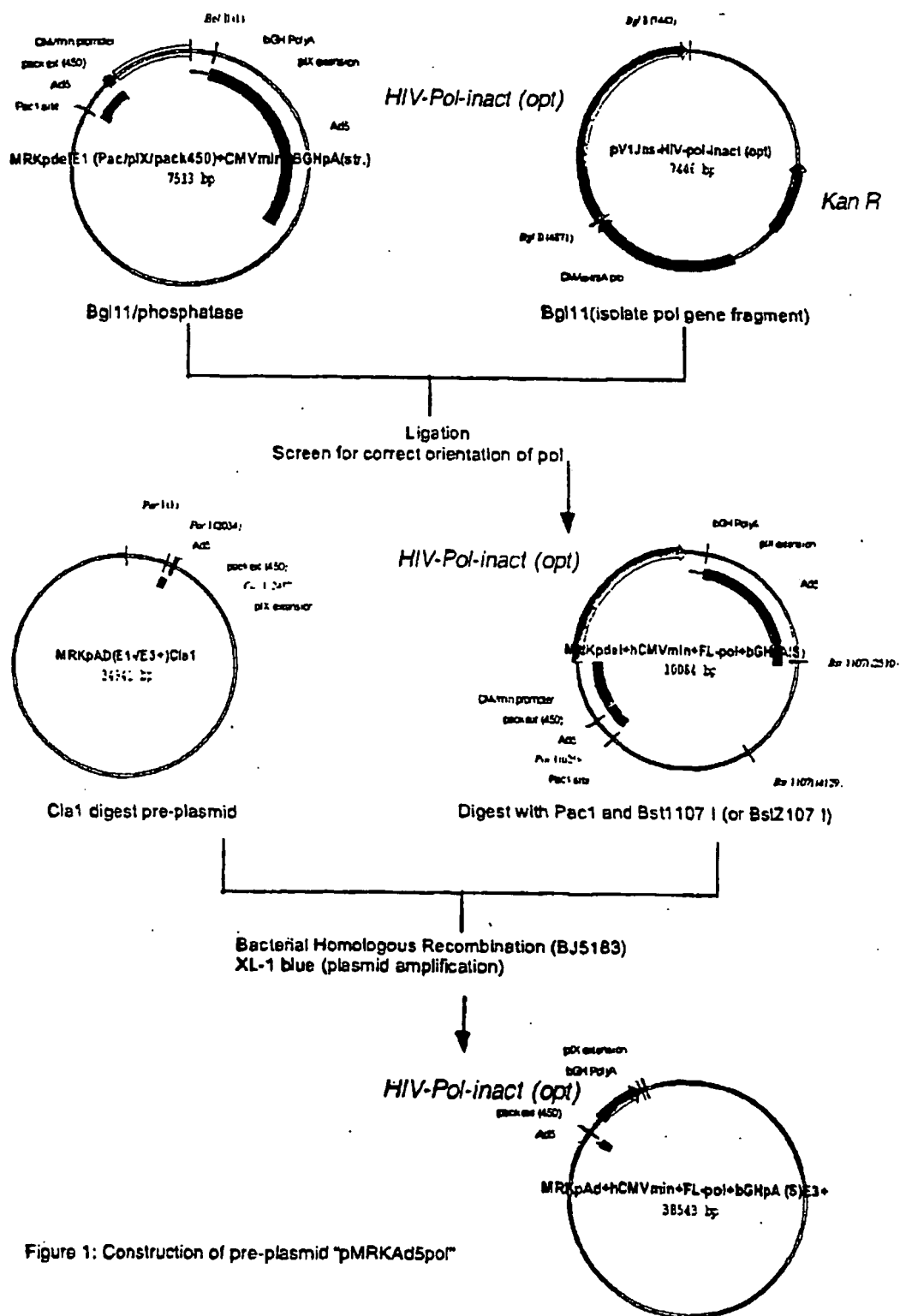


Figure 1: Construction of pre-plasmid "pMRKAd5pol"

FIGURE 22

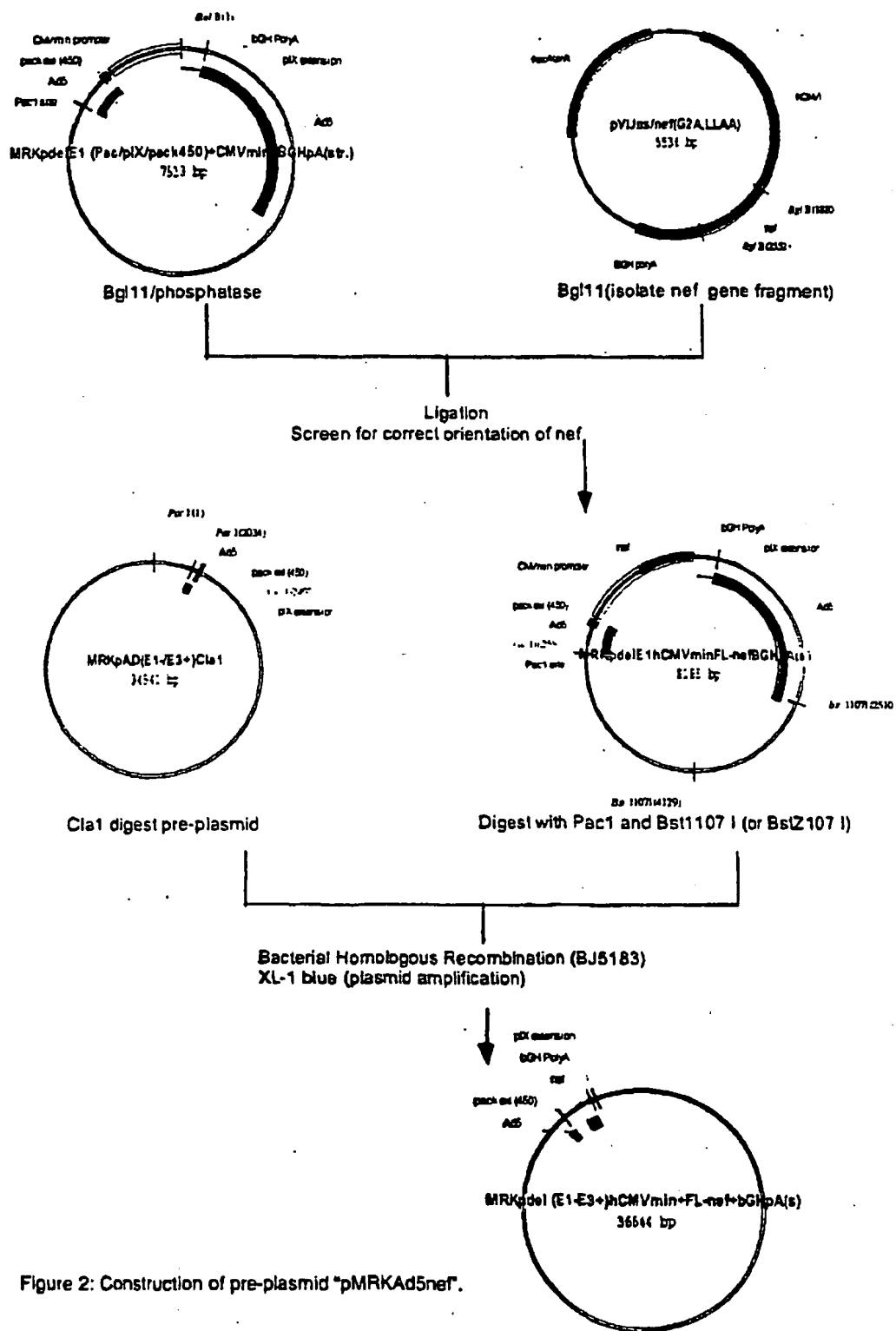
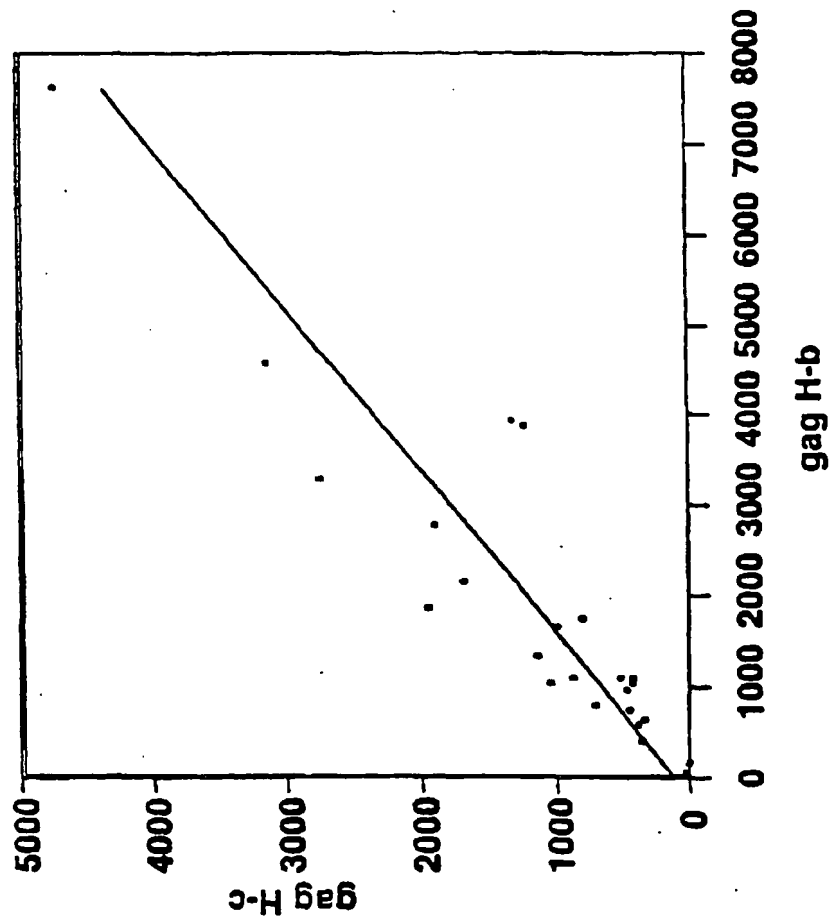


Figure 2: Construction of pre-plasmid "pMRKAd5nef".

FIGURE 23

Comparison of Clade B vs. Clade C Anti-gag T Cell Responses in Clade B HIV-Infected Subjects



Linear Fit

$$\text{gag H-c} = 111.603 + 0.55866 \text{ gag H-b}$$

Summary of Fit

RSquare	0.816775
RSquare Adj	0.80914
Root Mean Square Error	474.9639
Mean of Response	1158.115
Observations (or Sum Wgts)	26

Comparison of Clade B vs. Clade C Anti-nef T Cell Responses in Clade B HIV-Infected Subjects

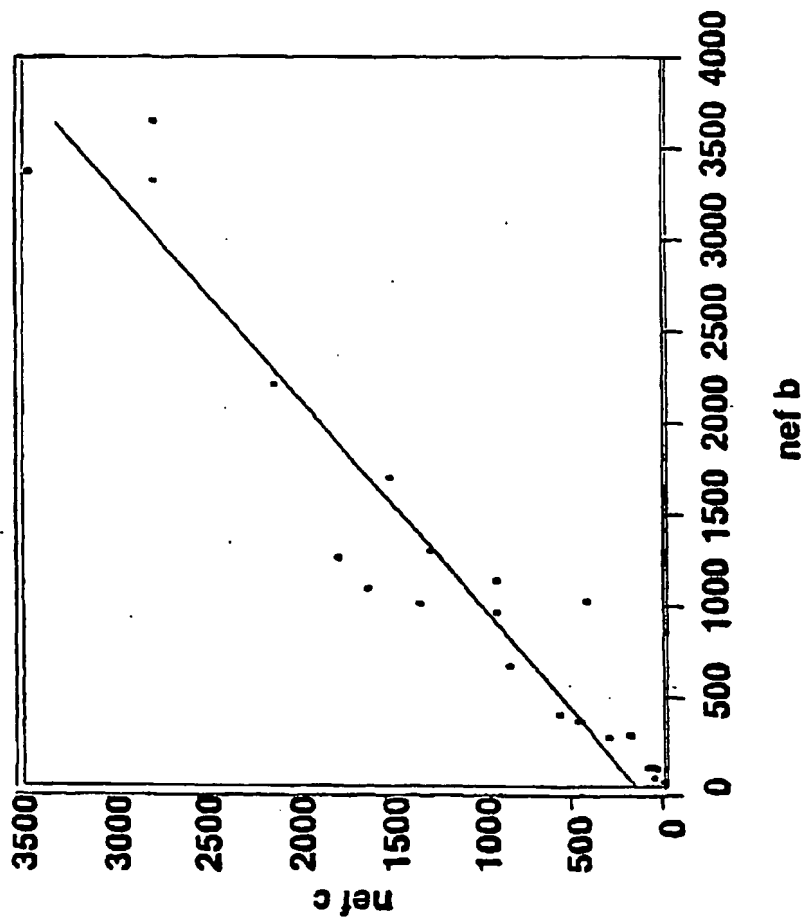


FIGURE 25

MRKAd5pol MER1062
(MRKAd5 Pre-Adenoviral Vector Containing the IA opt pol Coding Region)

```

1  CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG
   GTAGTAGTTA TTATATGGAA TAAARCTTAA CTTCGGTTAT ACTATTACTC

51  GGGGTGGAGT TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG
   CCCCACCTCA AACACTGCAC CGCGCCCCGC ACCCTTGCCC CGCCCACTGC

101 TAGTAGTGTG GCGGAAGTGT GATGTTGCAA GTGTGGCGGA ACACATGTAA
   ATCATCACAC CGCCTTCACA CTACAACGTT CACACCGCCT TGTGTACATT

151 GCGACGGATG TGGCAAAAGT GACGTTTTTG GTGTGCGCCG GTGTACACAG
   CGCTGCCCTAC ACCGTTTTCA CTGCAAAAAC CACACGCGGC CACATGTGTC

201 GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG TAAATTTGGG
   CTTCACTGTT AAAAGCGCGC CAAAATCCGC CTACAACATC ATTTAAACCC

251 CGTAACCGAG TAAGATTGGG CCATTTTCGC GGGAAACTG AATAAGAGGA
   GCATTGGCTC ATTCTAAACC GGTAAAAGCG CCCTTTTGAC TTATTCTCCT

301 AGTGAAATCT GAATAATTTT GTGTTACTCA TAGCGCGTAA TATTTGTCTA
   TCACCTTTAGA CTTATTAAAA CACAATGAGT ATCGCGCATT ATAAACAGAT

351 GGGCCGCGGG GACTTTGACC GTTACGTGG AGACTCGCCC AGGTGTTTTT
   CCGGCGCCCC CTGAACTGG CAAATGCACC TCTGAGCGGG TCCACAAAAA

401 CTCAGGTGTT TTCCGCGTTC CGGGTCAAAG TTGGCGTTTT ATTATTATAG
   GAGTCCACAA AAGGCGCAAG GCCCAGTTTC AACCGCAAAA TAATAATATC

451 GCGGCGCGGA TCCATTGCAT ACGTTGTATC CATATCATAA TATGTACATT
   CGCGGGCGCT AGSTAACGTA TGCAACATAG GTATAGTATT ATACATGTAA

501 TATATTGGCT CATGTCCAAC ATTACCGCCA TGTTGACATT GATTATTGAC
   ATATAACCGA GTACAGGTTG TAATGGCGGT ACAACTGTAA CTAATAACTG

551 TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTTCAT AGCCCATATA
   ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT

601 TGGAGTTCGG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG
   ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC

651 CCCAACGACC CCCGCCCAT TACGTCAATA ATGACGTATG TTCCCATAGT
   GGGTTGCTGG GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA

701 AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT
   TTGCGGTTAT CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

751 AAACTGCCCC CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTACGCCC
   TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCATGCGGG

801 CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCAGTA
   GGATAACTGC AGTTACTGCC ATTTACGGGG CGGACCGTAA TACGGGTCTT

851 CATGACCTTA TGGGACTTTC CTAATTGGCA GTACATCTAC GTATTAGTCA
   GTACTGGAAT ACCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT

```

Figure 26A

901 TCGCTATTAC CATGGTGATG CGGTTTTGGC AGTACATCAA TGGGCGTGGA
AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

951 TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA
ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT

1001 TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA
ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

1051 ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG
TGTGAGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

1101 GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1151 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC
GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTGCG

1201 TCCGCGGCCG GGAACGGTGC ATTGGAACGC GGATTCCCCG TGCCAAGAGT
AGGCGCCGCG CCTTGCCACG TAACCTTGCG CCTAAGGGGC ACGGTTCTCA

1251 GAGATCTACC ATGGCCCCCA TCTCCCCCAT TGAGACTGTG CCTGTGAAGC
CTCTAGATGG TACCGGGGGT AGAGGGGGTA ACTCTGACAC GGACACTTCG

1301 TGAAGCCTGG CATGGATGGC CCCAAGGTGA AGCAGTGGCC CCTGACTGAG
ACTTCGGACC GTACCTACCG GGGTTCCACT TCGTCACCGG GGACTGACTC

1351 GAGAAGATCA AGGCCCTGGT GGAAATCTGC ACTGAGATGG AGAAGGAGGG
CTCTTCTAGT TCCGGGACCA CCTTTAGACG TGACTCTACC TCTTCCTCCC

1401 CAAAATCTCC AAGATTGGCC CCGAGAACCC CTACAACACC CCTGTGTTTG
GTTTTAGAGG TTCTAACCGG GGCTCTTGGG GATGTTGTGG GGACACAAAC

1451 CCATCAAGAA GAAGGACTCC ACCAAGTGGA GGAAGCTGGT GGACTTCAGG
GGTAGTTCTT CTTCCTGAGG TGGTTCACCT CCTTCGACCA CCTGAAGTCC

1501 GAGCTGAACA AGAGGACCCA GGACTTCTGG GAGGTGCAGC TGGGCATCCC
CTCGACTTGT TCTCTGGGT CCTGAAGACC CTCCACGTCG ACCCGTAGGG

1551 CCACCCCGCT GGCCTGAAGA AGAAGAAGTC TGTGACTGTG CTGGCTGTGG
GGTGGGGCGA CCGGACTTCT TCTTCTTCAG AACTGACAC GACCGACACC

1601 GGGATGCCTA CTTCTCTGTG CCCCTGGATG AGGACTTCAG GAAGTACACT
CCCTACGGAT GAAGAGACAC GGGGACCTAC TCCTGAAGTC CTTTCATGTA

1651 GCCTTCACCA TCCCCTCCAT CAACAATGAG ACCCTGGCA TCAGGTACCA
CGGAAGTGGT AGGGGAGGTA GTTGTTACTC TGGGGACCGT AGTCCATGGT

1701 GTACAATGTG CTGCCCCAGG GCTGGAAGGG CTCCCCTGCC ATCTTCCAGT
CATGTTACAC GACGGGGTCC CGACCTTCCC GAGGGGACGG TAGAAGGTCA

1751 CCTCCATGAC CAAGATCCTG GAGCCCTTCA GGAAGCAGAA CCCTGACATT
GGAGGTACTG GTTCTAGGAC CTCGGGAAGT CCTTCGTCTT GGGACTGTAA

1801 GTGATCTACC AGTACATGGC TGCCCTGTAT GTGGGCTCTG ACCTGGAGAT
CACTAGATGG TCATGTACCG ACGGGACATA CACCCGAGAC TGGACCTCTA

Figure 24B

1901 GGGGCCTGAC CACCCCTGAC AAGAAGCACC AGAAGGAGCC CCCCTTCCTG
 CCCC GGACTG GTGGGGACTG TTCTTCGTGG TCTTCCTCGG GGGGAAGGAC
 1951 TGGATGGGCT ATGAGCTGCA CCCCACAAAG TGGACTGTGC AGCCCATTGT
 ACCTACCCGA TACTCGACGT GGGGCTGTTC ACCTGACACG TCGGGTAACA
 2001 GCTGCCTGAG AAGGACTCCT GGACTGTGAA TGACATCCAG AAGCTGGTGG
 CGACGGACTC TTCCTGAGGA CCTGACACTT ACTGTAGGTC TTCGACCACC
 2051 GCAAGCTGAA CTGGGCCTCC CAAATCTACC CTGGCATCAA GGTGAGGCAG
 CGTTCGACTT GACCCGGAGG GTTTAGATGG GACCGTAGTT CCACTCCGTC
 2101 CTGTGCAAGC TGCTGAGGGG CACCAAGGCC CTGACTGAGG TGATCCCCCT
 GACACGTTCG ACGACTCCCC GTGGTTCGGG GACTGACTCC ACTAGGGGGA
 2151 GACTGAGGAG GCTGAGCTGG AGCTGGCTGA GAACAGGGAG ATCCTGAAGG
 CTGACTCCTC CGACTCGACC TCGACCGACT CTTGTCCCTC TAGGACTTCC
 2201 AGCCTGTGCA TGGGGTGTAC TATGACCCCT CCAAGGACCT GATTGCTGAG
 TCGGACACGT ACCCCACATG ATACTGGGGA GGTTCCTGGA CTAACGACTC
 2251 ATCCAGAAGC AGGGCCAGGG CCAGTGGACC TACCAAATCT ACCAGGAGCC
 TAGGTCTTCG TCCCGGTCCC GGTACCTGG ATGGTTTAGA TGGTCTCGG
 2301 CTTCAGAAGC CTGAAGACTG GCAAGTATGC CAGGATGAGG GGGGCCACAC
 GAAGTTCTTG GACTTCTGAC CGTTCATACG GTCCTACTCC CCCC GGGTGT
 2351 CCAATGATGT GAAGCAGCTG ACTGAGGCTG TGCAGAAGAT CACCACTGAG
 GGTTACTACA CTTCGTCGAC TGACTCCGAC ACGTCTTCTA GTGGTGACTC
 2401 TCCATTGTGA TCTGGGGCAA GACCCCAAG TTCAAGCTGC CCATCCAGAA
 AGGTAACACT AGACCCCGTT CTGGGGGTTC AAGTTCGACG GGTAGGTCTT
 2451 GGAGACCTGG GAGACCTGGT GGACTGAGTA CTGGCAGGCC ACCTGGATCC
 CCTCTGGACC CTCTGGACCA CCTGACTCAT GACCGTCCGG TGGACCTAGG
 2501 CTGAGTGGGA GTTTGTGAAC ACCCCCCCCC TGGTGAAGCT GTGGTACCAG
 GACTCACCTT CAAACACTTG TGGGGGGGGG ACCACTTCGA CACCATGGTC
 2551 CTGGAGAAGG AGCCCATTGT GGGGGCTGAG ACCTTCTATG TGGCTGGGGC
 GACCTCTTCC TCGGGTAACA CCCC GACTC TGGGAAGATAC ACCGACCCCG
 2601 TGCCAACAGG GAGACCAAGC TGGGCAAGGC TGGCTATGTG ACCAACAGGG
 ACGGTTGTCC CTCTGGTTCG ACCCGTTCCG ACCGATACAC TGGTTGTCCC
 2651 GCAGGCAGAA GGTGGTGACC CTGACTGACA CCACCAACCA GAAGACTGCC
 CGTCCGTCTT CCACCACTGG GACTGACTGT GGTGGTTGGT CTTCTGACGG
 2701 CTCCAGGCCA TCTACCTGGC CCTCCAGGAC TCTGGCCTGG AGGTGAACAT
 GAGGTCCGGT AGATGGACCG GGAGGTCCTG AGACCGGACC TCCACTTGTA
 2751 TGTGACTGCC TCCCAGTATG CCCTGGGCAT CATCCAGGCC CAGCCTGATC
 ACAC TGACGG AGGGTCATAC GGGACCCGTA GTAGGTCCGG GTCGGACTAG

Figure 26C

2851 GAGAAGGTGT ACCTGGCCTG GGTGCCTGCC CACAAGGGCA TTGGGGGCAA
CTCTTCCACA TGGACCGGAC CCACGGACGG GTGTTCCCGT AACCCCCGTT

2901 TGAGCAGGTG GACAAGCTGG TGTCTGCTGG CATCAGGAAG GTGCTGTTCC
ACTCGTCCAC CTGTTTCGACC ACAGACGACC GTAGTCCTTC CACGACAAGG

2951 TGGATGGCAT TGACAAGGCC CAGGATGAGC ATGAGAAGTA CCACTCCAAC
ACCTACCGTA ACTGTTCCGG GTCTACTCG TACTCTTCAT GGTGAGGTTG

3001 TGGAGGGCTA TGGCCTCTGA CTTCAACCTG CCCCCTGTGG TGGCTAAGGA
ACCTCCCAGT ACCGGAGACT GAAGTTGGAC GGGGGACACC ACCGATTCTT

3051 GATTGTGGCC TCCTGTGACA AGTGCCAGCT GAAGGGGGAG GCCATGCATG
CTAACACCGG AGGACACTGT TCACGGTCGA CTTCCCCCTC CGGTACGTAC

3101 GGCAGGTGGA CTGCTCCCCT GGCATCTGGC AGCTGGCCTG CACCCACCTG
CCGTCCACCT GACGAGGGGA CCGTAGACCG TCGACCGGAC GTGGGTGGAC

3151 GAGGGCAAGG TGATCCTGGT GGCTGTGCAT GTGGCCTCCG GCTACATTGA
CTCCCGTTCC ACTAGGACCA CCGACACGTA CACCGGAGGC CGATGTAAC

3201 GGCTGAGGTG ATCCCTGCTG AGACAGGCCA GGAGACTGCC TACTTCCTGC
CCGACTCCAC TAGGGACGAC TCTGTCCGGT CCTCTGACGG ATGAAGGACG

3251 TGAAGCTGGC TGGCAGGTGG CCTGTGAAGA CCATCCACAC TGCCAATGGC
ACTTCGACCG ACCGTCCACC GGACACTTCT GGTAGGTGTG ACGGTTACCG

3301 TCCAACCTCA CTGGGGCCAC AGTGAGGGCT GCCTGCTGGT GGGCTGGCAT
AGGTTGAAGT GACCCCGGTG TCACTCCCGA CGGACGACCA CCCGACCGTA

3351 CAAGCAGGAG TTTGGCATCC CCTACAACCC CCAGTCCCAG GGGGTGGTGG
GTTCTCCTC AAACCGTAGG GGATGTTGGG GGTGAGGGTC CCCCACCACC

3401 CCTCCATGAA CAAGGAGCTG AAGAAGATCA TTGGGCAGGT GAGGGACCAG
GGAGGTACTT GTTCCTCGAC TTCTTCTAGT AACCCGTCCA CTCCCTGGTC

3451 GCTGAGCACC TGAAGACAGC TGTGCAGATG GCTGTGTTCA TCCACAACCT
CGACTCGTGG ACTTCTGTCTG ACACGTCTAC CGACACAAGT AGGTGTTGAA

3501 CAAGAGGAAG GGGGGCATCG GGGGCTACTC CGCTGGGGAG AGGATTGTGG
GTTCTCCTTC CCCCCGTAGC CCCCAGTAGG GCGACCCCTC TCCTAACACC

3551 ACATCATTGC CACAGACATC CAGACCAAGG AGCTCCAGAA GCAGATCACC
TGTAAGTAAAG GTGTCTGTAG GTCTGGTTCC TCGAGGTCTT CGTCTAGTGG

3601 AAGATCCAGA ACTTCAGGGT GTACTACAGG GACTCCAGGA ACCCCCTGTG
TTCTAGGTCT TGAAGTCCCA CATGATGTCC CTGAGGTCTT TGGGGGACAC

3651 GAAGGGCCCT GCCAAGCTGC TGTGGAAGGG GGAGGGGGCT GTGGTGATCC
CTTCCCGGGA CGGTTCGACG ACACCTTCCC CCTCCCCCGA CACCACCTAGG

3701 AGGACAACCTC TGACATCAAG GTGGTGCCCA GGAGGAAGGC CAAGATCATC
TCCTGTTGAG ACTGTAGTTC CACCACGGGT CCTCCTTCCG GTTCTAGTAG

Figure 26 D

3801 GGATGAGGAC TAAAGCCCGG GCAGATCTGC TGTGCCTTCT AGTTGCCAGC
CCTACTCCTG ATTTCTGGGCC CGTCTAGACG ACACGGAAGA TCAACGGTCG

3851 CATCTGTTGT TTGCCCCCTCC CCCGTGCCTT CCTTGACCCT GGAAGGTGCC
GTAGACAACA AACGGGGAGG GGGCACGGAA GGAACGGGA CCTTCCACGG

3901 ACTCCCCTG TCCTTTCTTA ATAAAATGAG GAAATTGCAT CGCATTGTCT
TGAGGGTGAC AGGAAAGGAT TATTTTACTC CTTTAACGTA GCGTAACAGA

3951 GAGTAGGTGT CATTCTATTC TGGGGGGTGG GGTGGGGCAG GACAGCAAGG
CTCATCCACA GTAAGATAAG ACCCCCCACC CCACCCCGTC CTGTCGTTC

4001 GGGAGGATTG GGAAGACAAT AGCAGGCATG CTGGGGATGC GGTGGGCTCT
CCCTCCTAAC CCTTCTGTTA TCGTCCGTAC GACCCCTACG CCACCCGAGA

4051 ATGGCCGATC GCGCGCCCGT ACTGAAATGT GTGGGCGTGG CTTAAGGGTG
TACCGGCTAG CCGCGCGGCA TGACTTTACA CACCCGCACC GAATTCAC

4101 GGAAAGAATA TATAAGGTGG GGGTCTTATG TAGTTTTGTA TCTGTTTTGC
CCTTCTTAT ATATTCCACC CCCAGAATAC ATCAAAACAT AGACAAAACG

4151 AGCAGCCGCC GCCGCCATGA GCACCAACTC GTTTGATGGA AGCATTGTGA
TCGTCGGCGG CCGCGGTACT CGTGGTTGAG CAAACTACCT TCGTAACACT

4201 GCTCATATTT GACAACGCGC ATGCCCCCAT GGGCCGGGGT GCGTCAGAA
CGAGTATAAA CTGTTGCGCG TACGGGGGTA CCCGGCCCCA CGCAGTCTTA

4251 GTGATGGGCT CCAGCATTGA TGGTCGCCCC GTCCTGCCCG CAACTCTAC
CACTACCCGA GGTCGTAACCT ACCAGCGGGG CAGGACGGGC GTTTGAGATG

4301 TACCTTGACC TACGAGACCG TGTCTGGAAC GCCGTTGGAG ACTGCAGCCT
ATGGAACCTG ATGCTCTGGC ACAGACCTTG CGGCAACCTC TGACGTCGGA

4351 CCGCCCGCGC TTCAGCCGCT GCAGCCACCG CCCGCGGGAT TGTGACTGAC
GGCGGCGGCG AAGTCGGCGA CGTCGGTGGC GGGCGCCCTA ACACTGACTG

4401 TTTGCTTTCC TGAGCCCGCT TGCAAACAGT GCAGCTTCCC GTTCATCCGC
AAACGAAAGG ACTCGGGCGA ACGTTTGTCA CGTCGAAGGG CAAGTAGGCG

4451 CCGCGATGAC AAGTTGACGG CTCTTTTGGC ACAATTGGAT TCTTTGACCC
GGCGCTACTG TTCAACTGCC GAGAAAACCG TGTTAACCTA AGAACTGGG

4501 GGGAACTTAA TGTCGTTTCT CAGCAGCTGT TGGATCTGCG CCAGCAGGTT
CCCTTGAATT ACAGCAAAGA GTCGTCGACA ACCTAGACGC GGTGCTCCAA

4551 TCTGCCCTGA AGGCTTCCTC CCCTCCCAAT GCGGTTTAAA ACATAAATAA
AGACGGGACT TCCGAAGGAG GGGAGGGTTA CGCCAAATTT TGTATTTAT

4601 AAAACCAGAC TCTGTTTGGA TTTGGATCAA GCAAGTGTCT TGCTGTCTTT
TTTTGGTCTG AGACAAACCT AAACCTAGTT CGTTCACAGA ACGACAGAAA

4651 ATTTAGGGGT TTTGCGCGCG CGGTAGGCCC GGGACCAGCG GTCTCGGTCG
TAAATCCCA AAACGCGCGC GCCATCCGGG CCCTGGTCGC CAGAGCCAGC

Figure 26E

4751 GTTCAGATAC ATGGGCATAA GCCCGTCTCT GGGGTGGAGG TAGCACCACCT
 CAAGTCTATG TACCCGTATT CGGGCAGAGA CCCCACCTCC ATCGTGGTGA
 4801 GCAGAGCTTC ATGCTGCGGG GTGGTGTGT AGATGATCCA GTCGTAGCAG
 CGTCTCGAAG TACGACGCCC CACCACAACA TCTACTAGGT CAGCATCGTC
 4851 GAGCGCTGGG CGTGGTGCCT AAAAATGTCT TTCAGTAGCA AGCTGATTGC
 CTCGCGACCC GCACCACGGA TTTTACAGA AAGTCATCGT TCGACTAACG
 4901 CAGGGGCAGG CCCTTGGTGT AAGTGTTTAC AAAGCGGTTA AGCTGGGATG
 GTCCCCGTCC GGAACCACA TTCACAAATG TTTCGCCAAT TCGACCCTAC
 4951 GGTGCATACG TGGGGATATG AGATGCATCT TGGACTGTAT TTTAGGTTG
 CCACGTATGC ACCCCTATAC TCTACGTAGA ACCTGACATA AAAATCCAAC
 5001 GCTATGTTCC CAGCCATATC CCTCCGGGGA TTCATGTTGT GCAGAACCAC
 CGATACAAGG GTCGGTATAG GGAGGCCCTT AAGTACAACA CGTCTTGGTG
 5051 CAGCACAGTG TATCCGGTGC ACTTGGGAAA TTTGTCATGT AGCTTAGAAG
 GTCGTGTCAC ATAGGCCACG TGAACCTTTT AAACAGTACA TCGAATCTTC
 5101 GAAATGCGTG GAAGAACTTG GAGACGCCCT TGTGACCTCC AAGATTTTCC
 CTTTACGCAC CTTCTTGAAC CTCTGCGGGA AACTGGAGG TTCTAAAAGG
 5151 ATGCATTCTG CCATAATGAT GGCAATGGGC CCACGGGCGG CGGCCTGGGC
 TACGTAAGCA GGTATTACTA CCGTTACCCG GGTGCCCCGC GCCGGACCCG
 5201 GAAGATATTT CTGGGATCAC TAACGTCATA GTTGTGTTCC AGGATGAGAT
 CTCTATAAA GACCCTAGTG ATTGCAGTAT CAACACAAGG TCCTACTCTA
 5251 CGTCATAGGC CATTTTACCA AAGCGCGGGC GGAGGGTGCC AGACTGCGGT
 GCAGTATCCG GTAAAAATGT TTCGCGCCCG CCTCCACGG TCTGACGCCA
 5301 ATAATGGTTC CATCCGGCCC AGGGGCGTAG TTACCCTCAC AGATTTGCAT
 TATTACCAAG GTAGGCCGGG TCCCCGCATC AATGGGAGTG TCTAAACGTA
 5351 TTCCACGCT TTGAGTTCAG ATGGGGGAT CATGTCTACC TGCGGGGCGA
 AAGGTGCGA AACTCAAGTC TACCCCCCTA GTACAGATGG ACGCCCCGCT
 5401 TGAAGAAAAC GGTTCGCGG GTAGGGGAGA TCAGCTGGGA AGAAAGCAGG
 ACTTCTTTTG CCAAAGGCC CATCCCCTCT AGTCGACCCT TCTTTCGTCC
 5451 TTCCTGAGCA GCTGCGACTT ACCGAGCCG GTGGGCCCCG AAATCACACC
 AAGGACTCGT CGACGCTGAA TGGCGTCGCG CACCCGGGCA TTTAGTGTGG
 5501 TATTACCGGC TGCAACTGGT AGTTAAGAGA GCTGCAGCTG CCGTCATCCC
 ATAATGGCCG ACGTTGACCA TCAATTCTCT CGACGTCGAC GGCAGTAGGG
 5551 TGAGCAGGGG GGCCACTTCG TTAAGCATGT CCCTGACTCG CATGTTTTCC
 ACTCGTCCCC CCGGTGAAGC AATTCGTACA GGGACTGAGC GTACAAAAGG
 5601 CTGACCAAAT CCGCCAGAAG GCGCTCGCCG CCCAGCGATA GCAGTTCTTG
 GACTGGTTTA GGCGGTCTTC CGCGAGCGGC GGGTCGCTAT CGTCAAGAAC

Figure 26 F

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5701 TTTTGAGCGT TTGACCAAGC AGTTCCAGGC GGTCCCACAG CTCGGTCACC
      AAAACTCGCA AACTGGTTCG TCAAGGTCCG CCAGGGTGTC GAGCCAGTGG

5751 TGCTCTACGG CATCTCGATC CAGCATATCT CCTCGTTTCG CGGGTTGGGG
      ACGAGATGCC GTAGAGCTAG GTCGTATAGA GGAGCAAAGC GCCCAACCCC

5801 CGGCTTTTCG TGTACGGCAG TAGTCGGTGC TCGTCCAGAC GGGCCAGGGT
      GCCGAAAGCG ACATGCCGTC ATCAGCCACG AGCAGGTCTG CCCGGTCCCA

5851 CATGTCTTTC CACGGGCGCA GGGTCCTCGT CAGCGTAGTC TGGGTCACGG
      GTACAGAAAG GTGCCCGCGT CCCAGGAGCA GTCGCATCAG ACCCAGTGCC

5901 TGAAGGGGTG CGCTCCGGGC TGC CGCTGG CCAGGGTGCG CTTGAGGCTG
      ACTTCCCAC GCGAGGCCG ACGCGCGACC GGTCCCACGC GAACTCCGAC

5951 GTCCTGCTGG TGCTGAAGCG CTGCCGGTCT TCGCCCTGCG CGTCGGCCAG
      CAGGACGACC ACGACTTCGC GACGGCCAGA AGCGGGACGC GCAGCCGGTC

6001 GTAGCATTTG ACCATGGTGT CATAGTCCAG CCCCTCCGCG GCGTGGCCCT
      CATCGTAAAC TGGTACCACA GTATCAGGTC GGGGAGGCGC CGCACCGGGA

6051 TGGCGCGCAG CTTGCCCTTG GAGGAGGCGC CGCACGAGGG GCAGTGCAGA
      ACCGCGCGTC GAACGGGAAC CTCCTCCGCG GCGTGCTCCC CGTCACGTCT

6101 CTTTTGAGGG CGTAGAGCTT GGGCGCGAGA AATACCGATT CCGGGGAGTA
      GAAAACCTCC GCATCTCGAA CCCGCGCTCT TTATGGCTAA GGCCCCCTCAT

6151 GGCATCCGCG CCGCAGGCC CCGCAGACGGT CTCGCATTCC ACGAGCCAGG
      CCGTAGGCGC GCGTCCGGG GCGTCTGCCA GAGCGTAAGG TGCTCGGTCC

6201 TGAGCTCTGG CCGTTCGGGG TCAAAAACCA GGTTTCCCC ATGCTTTTTG
      ACTCGAGACC GGCAAGCCCC AGTTTTTGGT CCAAAGGGGG TACGAAAAAC

6251 ATGCGTTTCT TACCTCTGGT TTCCATGAGC CGGTGTCCAC GCTCGGTGAC
      TACGCAAAGA ATGGAGACCA AAGGTACTCG GCCACAGGTG CGAGCCACTG

6301 GAAAAGGCTG TCCGTGTCCC CGTATACAGA CTTGAGAGGC CTGTCCTCGA
      CTTTTCGAC AGGCACAGGG GCATATGTCT GAACTCTCCG GACAGGAGCT

6351 GCGGTGTTCC GCGGTCTCTC TCGTATAGAA ACTCGGACCA CTCTGAGACA
      CGCCACAAGG CGCCAGGAGG AGCATATCTT TGAGCCTGGT GAGACTCTGT

6401 AAGGCTCGCG TCCAGGCCAG CACGAAGGAG GCTAAGTGGG AGGGGTAGCG
      TTCCGAGCGC AGGTCCGGTC GTGCTTCCTC CGATTCAACC TCCCCATCGC

6451 GTCGTTGTCC ACTAGGGGGT CCACTCGCTC CAGGGTGTGA AGACACATGT
      CAGCAACAGG TGATCCCCCA GGTGAGCGAG GTCCCACT TCTGTGTACA

6501 CGCCCTCTTC GGCATCAAGG AAGGTGATTG GTTTGTAGGT GTAGGCCACG
      GCGGGAGAAG CCGTAGTTCC TTCCACTAAC CAAACATCCA CATCCGGTGC

6551 TGACCGGGTG TTCCTGAAGG GGGGCTATAA AAGGGGGTGG GGGCGCGTTC
      ACTGGCCAC AAGGACTTCC CCCCATATT TTCCCCACC CCCGCGCAAG

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Figure 266

6651 AGTACTCCCT CTGAAAAGCG GGCATGACTT CTGCGCTAAG ATTGTCA GTT
TCATGAGGGA GACTTTTCGC CCGTACTGAA GACGCGATTC TAACAGTCAA

6701 TCCAAAAACG AGGAGGATTT GATATTCACC TGGCCCGCGG TGATGCCTTT
AGGTTTTTGC TCCTCCTAAA CTATAAGTGG ACCGGGCGCC ACTACGGA

6751 GAGGGTGGCC GCATCCATCT GGTGAGAAAA GACAATCTTT TTGTGTCAA
CTCCACCGG CGTAGGTAGA CCAGTCTTTT CTGTAGAAAA AACACAGTT

6801 GCTTGGTGGC AAACGACCCG TAGAGGGCGT TGGACAGCAA CTGGCGATG
CGAACACCG TTTGCTGGGC ATCTCCCGCA ACCTGTCGTT GAACCGCTAC

6851 GAGCGCAGGG TTTGGTTTTT GTCGCGATCG GCGCGCTCCT TGGCCGCGAT
CTCGCGTCCC AAACCAAAAA CAGCGCTAGC GCGCGAGGA ACCGGCGCTA

6901 GTTTAGCTGC ACGTATTCGC GCGCAACGCA CCGCCATTCT GGAAAGACGG
CAATCGACG TGCATAAGCG CGCGTTGCGT GCGGTAAGC CCTTCTGCC

6951 TGGTGCCTC GTCGGGACC AGGTGCACGC GCCAACCGCG GTTGTGCAGG
ACCACGCGAG CAGCCCGTGG TCCACGTGCG CGGTTGGCGC CAACACGTCC

7001 GTGACAAGGT CAACGCTGGT GGCTACCTCT CCGCGTAGGC GCTCGTTGGT
CACTGTTCCA GTTGCACCA CCGATGGAGA GCGCATCCG CGAGCAACCA

7051 CCAGCAGAGG CGGCCGCCCT TGCAGGAGCA GAATGGCGGT AGGGGGTCTA
GGTCGTCTCC GCCGGCGGGA ACGCGCTCGT CTTACCGCA TCCCCAGAT

7101 GCTGCGTCTC GTCCGGGGGG TCTGCGTCCA CCGTAAAGAC CCCGGGCGC
CGACGAGAG CAGGCCCCC AGACGAGGT GCCATTCTG GGGCCCGTCG

7151 AGGCGCGCGT CGAAGTAGTC TATCTTGCACT CTTGCAAGT CTAGCGCTG
TCCGCGCGCA GCTTCATCAG ATAGAACGTA GGAACGTTCA GATCGCGGAC

7201 CTGCCATGCG CGGGCGGCAA GCGCGCGCTC GTATGGGTTG AGTGGGGGAC
GACGGTACGC GCCCGCCGTT CCGCGCGGAG CATACCCAAC TCACCCCTG

7251 CCCATGGCAT GGGGTGGGTG AGCGCGGAGG CGTACATGCC GCAAATGTCG
GGGTACCGTA CCCACCCAC TCGCGCCTCC GCATGTACGG CGTTTACAGC

7301 TAAACGTAGA GGGGCTCTCT GAGTATTCCA AGATATGTAG GGTAGCATCT
ATTTGCATCT CCCCAGAGA CTCATAAGGT TCTATACATC CCATCGTAGA

7351 TCCACCGCGG ATGCTGGCGC GCACGTAATC GTATAGTTCT TGCGAGGGAG
AGGTGGCGCC TACGACCGCG CGTGCAATTAG CATATCAAGC ACGCTCCCTC

7401 CGAGGAGGTC GGGACCGAGG TTGCTACGGG CGGGCTGCTC TGCTCGGAAG
GCTCCTCCAG CCTTGGCTCC AACGATGCCC GCCCGACGAG ACGAGCCTTC

7451 ACTATCTGCC TGAAGATGGC ATGTGAGTTG GATGATATGG TTGGACGCTG
TGATAGACGG ACTTCTACCG TACACTCAAC CTACTATACC AACCTGCGAC

7501 GAAGACGTTG AAGCTGGCGT CTGTGAGACC TACCGCGTCA CGCACGAAGG
CTTCTGCAAC TTCGACCGCA GACACTCTGG ATGGCGCAGT GCGTGCTTCC

Figure 26 H

7601 TCTAGGGCGC AGTAGTCCAG GGTTCCTTG ATGATGTCAT ACTTATCCTG
AGATCCCGCG TCATCAGGTC CCAAAGGAAC TACTACAGTA TGAATAGGAC

7651 TCCCTTTTTT TTCCACAGCT CGCGGTTGAG GACAACTCT TCGCGGTCTT
AGGGAAAAAA AAGGTGTCGA GCGCCAAC TC GTTTGAGA AGCGCCAGAA

7701 TCCAGTACTC TTGGATCGGA AACCCGTCGG CCTCCGAACG GTAAGAGCCT
AGGTCATGAG AACCTAGCCT TTGGGCAGCC GGAGGCTTGC CATTCCTCGGA

7751 AGCATGTAGA ACTGGTTGAC GGCCTGGTAG GCGCAGCATC CCTTTTCTAC
TCGTACATCT TGACCAACTG CCGGACCATC CGCGTCGTAG GGAAAAGATG

7801 GGGTAGCGCG TATGCCTGCG CGGCCTTCG GAGCGAGGTG TGGGTGAGCG
CCCATCGCGC ATACGGACGC GCCGGAAGGC CTCGCTCCAC ACCCACTCGC

7851 CAAAGGTGTC CCTGACCATG ACTTTGAGGT ACTGGTATTT GAAGTCAGTG
GTTTCCACAG GGACTGGTAC TGAAACTCCA TGACCATAAA CTTCAGTCAC

7901 TCGTCGCATC CGCCCTGCTC CCAGAGCAAA AAGTCCGTGC GCTTTTGGGA
AGCAGCGTAG GCGGGACGAG GGTCTCGTTT TTCAGGCACG CGAAAAACCT

7951 ACGCGGATTT GGCAGGGCGA AGGTGACATC GTTGAAGAGT ATCTTTCCCG
TGCGCCTAAA CCGTCCCGCT TCCACTGTAG CAACTTCTCA TAGAAAGGGC

8001 CGCGAGGCAT AAAGTTGCGT GTGATGCGGA AGGGTCCCGG CACCTCGGAA
GCGCTCCGTA TTCAACGCA CACTACGCCT TCCCAGGGCC GTGGAGCCTT

8051 CGGTGTGTTAA TTACCTGGGC GGCGAGCAG ATCTCGTCAA AGCCGTTGAT
GCCAACAAAT AATGGACCCG CCGCTCGTGC TAGAGCAGTT TCGGCAACTA

8101 GTTGTGGCCC ACAATGTAAA GTTCCAAGAA GCGCGGGATG CCCTTGATGG
CAACACCGGG TGTTACATTT CAAGGTTCTT CGCGCCCTAC GGGAAGTACC

8151 AAGGCAATTT TTTAAGTTCC TCGTAGGTGA GCTCTTCAGG GGAGCTGAGC
TTCCGTTAAA AAATCAAGG AGCATCCACT CGAGAAGTCC CTCGACTCG

8201 CCGTGCTCTG AAAGGGCCCA GTCTGCAAGA TGAGGGTTGG AAGCGACGAA
GGCACGAGAC TTCCCGGGT CAGACGTTCT ACTCCAACC TTCGCTGCTT

8251 TGAGCTCCAC AGGTCACGGG CCATTAGCAT TTGCAGGTGG TCGCGAAAGG
ACTCGAGGTG TCCAGTGCCC GGTAAATCGTA AACGTCCACC AGCGCTTTCC

8301 TCCTAAACTG GCGACCTATG GCCATTTTTT CTGGGGTGAT GCAGTAGAAG
AGGATTTGAC CGCTGGATAC CGGTAAAAAA GACCCCACTA CGTCATCTTC

8351 GTAAGCGGGT CTTGTTCCCA GCGGTCCCAT CCAAGGTTCTG CGGCTAGGTG
CATTCGCCCA GAACAAGGGT CGCCAGGGTA GGTTCGAAGC GCCGATCCAG

8401 TCGCGCGGCA GTCCTAGAG GCTCATCTCC GCCGAAC TTC ATGACCAGCA
AGCGCGCCGT CAGTGATCTC CGAGTAGAGG CGGCTTGAAG TACTGGTCGT

8451 TGAAGGGCAC GAGCTGCTTC CCAAAGGCC CCATCCAAGT ATAGGTCTCT
ACTTCCCGTG CTCGACGAAG GGTTCGCGG GGTAGGTTCA TATCCAGAGA

Figure 26I

8551 GAAGAACTGG ATCTCCCGCC ACCAATTGGA GGAGTGGCTA TTGATGTGGT
CTTCTTGACC TAGAGGGCGG TGGTTAACCT CCTCACCAGT AACTACACCA

8601 GAAAGTAGAA GTCCCTGCGA CGGGCCGAAC ACTCGTGCTG GCTTTTGTA
CTTTCATCTT CAGGGACGCT GCCCGGCTTG TGAGCACGAC CGAAAACATT

8651 AAACGTGCGC AGTACTGGCA GCGGTGCACG GGCTGTACAT CCTGCACGAG
TTTGCACGCG TCATGACCGT CGCCACGTGC CCGACATGTA GGACGTGCTC

8701 GTTGACCTGA CGACCGCGCA CAAGGAAGCA GAGTGGGAAT TTGAGCCCCCT
CAACTGGACT GCTGGCGCGT GTTCCTTCGT CTCACCCTTA AACTCGGGGA

8751 CGCCTGGCGG GTTTGGCTGG TGGTCTTCTA CTTGCGCTGC TTGTCCTTGA
GCGGACCGCC CAAACCGACC ACCAGAAGAT GAAGCCGACG AACAGGAAC

8801 CCGTCTGGCT GCTCGAGGGG AGTTACGGTG GATCGGACCA CCACGCCGCG
GGCAGACCGA CGAGCTCCCC TCAATGCCAC CTAGCCTGGT GGTGCGGCGC

8851 CGAGCCCCAA GTCCAGATGT CCGCGCGCGG CGGTCGGAGC TTGATGACAA
GCTCGGGTTT CAGGTCTACA GCGCGCGCGC GCCAGCCTCG AACTACTGTT

8901 CATCGCGCAG ATGGGAGCTG TCCATGGTCT GGAGCTCCCG CGGCGTCAGG
GTAGCGCGTC TACCCTCGAC AGGTACCAGA CCTCGAGGGC GCCGCAGTCC

8951 TCAGGCGGGA GCTCCTGCAG GTTTACCTCG CATAGACGGG TCAGGCGCGG
AGTCCGCCCT CGAGGACGTC CAAATGGAGC GTATCTGCCC AGTCCCAGCG

9001 GGCTAGATCC AGGTGATACC TAATTTCCAG GGGCTGGTTG GTGGCGGCGT
CCGATCTAGG TCCACTATGG ATTAAAGGTC CCCGACCAAC CACCGCCGCA

9051 CGATGGCTTG CAAGAGGCCG CATCCCCGCG GCGCGACTAC GGTACCGCGC
GCTACCGAAC GTTCTCCGGC GTAGGGGCGC CGCGCTGATG CCATGGCGCG

9101 GCGGGGCGGT GGGCCGCGGG GGTGTCCTTG GATGATGCAT CTAAAAGCGG
CCGCCCCGCA CCCGGCGCCC CCACAGGAAC CTACTACGTA GATTTTCGCG

9151 TGACGCGGGC GAGCCCCCGG AGGTAGGGGG GGCTCCGGAC CCGCCGGGAG
ACTGCGCCCG CTCGGGGGCC TCCATCCCCC CCGAGGCCTG GCGGGCCCTC

9201 AGGGGGCAGG GGCACGTCGG CGCCGCGCGC GGGCAGGAGC TGGTGCTGCG
TCCCCCGTCC CCGTGCAGCC GCGGCGCGCG CCCGTCTCG ACCACGACGC

9251 CGCGTAGGTT GCTGGCGAAC GCGACGACGC GCGGTTGAT CTCCTGAATC
GCGCATCCAA CGACCGCTTG CGCTGCTGCG CCGCCAACTA GAGGACTTAG

9301 TGGCGCCTCT GCGTGAAGAC GACGGGCCCC GTGAGCTTGA ACCTGAAAGA
ACCGCGGAGA CGCACTTCTG CTGCCCCGGC CACTCGAACT TGGACTTTCT

9351 GAGTTCGACA GAATCAATTT CGGTGTCGTT GACGGCGGCC TGGCGCAAAA
CTCAAGCTGT CTTAGTTAAA GCCACAGCAA CTGCCGCCGG ACCGCGTTTT

9401 TCTCCTGCAC GTCTCCTGAG TTGTCTTGAT AGGCGATCTC GGCCATGAAC
AGAGGACGTG CAGAGGACTC AACAGAACTA TCCGCTAGAG CCGGTACTTG

Figure 26 J

9501 GCGGCGGAGG TCGTTGGAAA TCGGGGCCAT GAGCTGCGAG AAGGCGTTGA
CCGCCGCTCC AGCAACCTTT ACGCCCGGTA CTCGACGCTC TTCCGCAACT

9551 GGCCTCCCTC GTTCCAGACG CGGCTGTAGA CCACGCCCCC TTCGGCATCG
CCGGAGGGAG CAAGGTCTGC GCCGACATCT GGTGCGGGGG AAGCCGTAGC

9601 CGGGCGCGCA TGACCACCTG CGCGAGATTG AGCTCCACGT GCCGGGCGAA
GCCCCGCGCT ACTGGTGGAC GCGCTCTAAC TCGAGGTGCA CGGCCCGCTT

9651 GACGGCGTAG TTTCGCAGGC GCTGAAAGAG GTAGTTGAGG GTGGTGGCGG
CTGCCGCATC AAAGCGTCCG CGACTTTCTC CATCAACTCC CACCACCGCC

9701 TGTGTTCTGC CACGAAGAAG TACATAACCC AGCGTCGCAA CGTGGATTGG
ACACAAGACG GTGCTTCTTC ATGTATTGGG TCGCAGCGTT GCACCTAAGC

9751 TTGATATCCC CCAAGGCCCTC AAGGCGCTCC ATGGCCTCGT AGAAGTCCAC
AACTATAGGG GGTTCGAGG TTCCGCGAGG TACCGGAGCA TCTTCAGGTG

9801 GCGGAAGTTG AAAAAGTGGG AGTTGCGCGC CGACACGGTT AACTCCTCCT
CCGCTTCAAC TTTTGGACCC TCAACGCGCG GCTGTGCCAA TTGAGGAGGA

9851 CCAGAAGACG GATGAGCTCG GCGACAGTGT CGCGCACCTC GCGCTCAAAG
GGTCTTCTGC CTACTCGAGC CGCTGTCACA GCGCGTGGAG CGCGAGTTTC

9901 GCTACAGGGG CCTCTTCTTC TTCTTCAATC TCCTCTTCCA TAAGGGCCTC
CGATGTCCCC GGAGAAGAAG AAGAAGTTAG AGGAGAAGGT ATTCGCGAG

9951 CCCTTCTTCT TCTTCTGGCG GCGGTGGGGG AGGGGGGACA CGGCGGCGAC
GGGAAGAAGA AGAAGACCGC CGCCACCCCC TCCCCCTGT GCCGCCGCTG

10001 GACGGCGCAC CGGGAGGCGG TCGACAAAGC GCTCGATCAT CTCCCCGCGG
CTGCCGCGTG GCCCTCCGCC AGCTGTTTCG CGAGCTAGTA GAGGGGCGCC

10051 CGACGGCGCA TGGTCTCGGT GACGGCGCGG CCGTTCTCGC GGGGGCGCAG
GCTGCCGCGT ACCAGAGCCA CTGCCGCGCC GGCAAGAGCG CCCCCGCGTC

10101 TTGGAAGACG CGCCCCGTCA TGTCCCGGTT ATGGGTTGGC GGGGGGCTGC
AACCTTCTGC GGCGGGCAGT ACAGGGCCAA TACCCAACCG CCCCCGACG

10151 CATGCGGCAG GGATACGGCG CTAACGATGC ATCTCAACAA TTGTTGTGTA
GTACGCCGTC CCTATGCCGC GATTGCTACG TAGAGTTGTT AACAACACAT

10201 GGTACTCCGC CGCCGAGGGA CCTGAGCGAG TCCGCATCGA CCGGATCGGA
CCATGAGGCG GCGGCTCCCT GGACTCGCTC AGGCGTAGCT GGCTAGCCT

10251 AAACCTCTCG AGAAAGGCGT CTAACCAGTC ACAGTCGCAA GGTAAGGTGA
TTTGAGAGC TCTTTCCGCA GATTGGTCAG TGTCAGCGTT CCATCCGACT

10301 GCACCGTGGC GGGCGGCAGC GGGCGGCGGT CGGGGTTGTT TCTGGCGGAG
CGTGGCACC GCGGCCGTCG CCGGCCGCCA GCCCAACAA AGACCGCCTC

10351 GTGCTGCTGA TGATGTAATT AAAGTAGGCG GTCTTGAGAC GCGGATGGT
CACGACGACT ACTACATTAA TTTTCATCCG CAGAACTCTG CCGCCTACCA

Figure 26 K

10451 CGGCCATGCC CCAGGCTTCG TTTTGACATC GGCGCAGGTC TTTGTAGTAG
 GCCGGTACGG GGTCCGAAGC AAAACTGTAG CCGCGTCCAG AAACATCATC
 10501 TCTTGCATGA GCCTTTCTAC CGGCACTTCT TCTTCTCCTT CCTCTTGTC
 AGAACGTACT CGGAAAGATG GCCGTGAAGA AGAAGAGGAA GGAGAACAGG
 10551 TGCATCTCTT GCATCTATCG CTGCGGCGGC GGCGGAGTTT GGCCGTAGGT
 ACGTAGAGAA CGTAGATAGC GACGCCGCCG CCGCCTCAA CCGGCATCCA
 10601 GGCGCCCTCT TCCTCCCATG CGTGTGACCC CGAAGCCCCCT CATCGGCTGA
 CCGCGGGAGA AGGAGGGTAC GCACACTGGG GCTTCGGGGA GTAGCCGACT
 10651 AGCAGGGGCTA GGTGCGCGAC AACGCGCTCG GCTAATATGG CCTGCTGCAC
 TCGTCCCGAT CCAGCCGCTG TTGCGCGAGC CGATTATACC GGACGACGTG
 10701 CTGCGTGAGG GTAGACTGGA AGTCATCCAT GTCCACAAAG CGGTGGTATG
 GACGCACTCC CATCTGACCT TCAGTAGGTA CAGGTGTTTC GCCACCATAC
 10751 CGCCCGTGTT GATGGTGTA GTGCAGTTGG CCATAACGGA CCAGTTAACC
 GCGGGCACAA CTACCACATT CACGTCAACC GGTATTGCC TGGTCAATTGC
 10801 GTCTGGTGAC CCGGCTGCGA GAGCTCGGTG TACCTGAGAC GCGAGTAAGC
 CAGACCACTG GGCCGACGCT CTCGAGCCAC ATGGACTCTG CGCTCATTCG
 10851 CCTCGAGTCA AATACGTAGT CGTTGCAAGT CCGCACCAGG TACTGGTATC
 GGAGCTCAGT TTATGCATCA GCAACGTTCA GCGGTGGTCC ATGACCATAG
 10901 CCACCAAAAA GTGCGGCGGC GGCTGGCGGT AGAGGGGCCA GCGTAGGGTG
 GGTGGTTTTT CACGCCGCCG CCGACCGCCA TCTCCCCGGT CGCATCCCAC
 10951 GCCGGGGCTC CGGGGGCGAG ATCTTCCAAC ATAAGGCGAT GATATCCGTA
 CCGCCCCGAG GCCCCCGCTC TAGAAGGTTG TATTCCGCTA CTATAGGCAT
 11001 GATGTACCTG GACATCCAGG TGATGCCGGC GGCGGTGGTG GAGGCGCGCG
 CTACATGGAC CTGTAGGTCC ACTACGGCCG CCGCCACCAC CTCGCGCGCG
 11051 GAAAGTCGCG GACGCGGTTC CAGATGTTGC GCAGCGGCAA AAAGTGCTCC
 CTTTCAGCGC CTGCGCCAAG GTCTACAACG CGTCGCCGTT TTTCACGAGG
 11101 ATGGTCGGGA CGCTCTGGCC GGTCAGGCGC GCGCAATCGT TGACGCTCTA
 TACCAGCCCT GCGAGACCGG CCAGTCCGCG CCGGTTAGCA ACTGCGAGAT
 11151 GACCGTGCAA AAGGAGAGCC TGTAAGCGGG CACTCTTCCG TGGTCTGGTG
 CTGGCACGTT TTCCTCTCGG ACATTCGCCC GTGAGAAGGC ACCAGACCAC
 11201 GATAAATTCG CAAGGGTATC ATGGCGGACG ACCGGGGTTC GAGCCCCGTA
 CTATTTAAGC GTTCCCATAG TACCGCCTGC TGGCCCCAAG CTCGGGGCAT
 11251 TCCGGCCGTC CGCCGTGATC CATGCGGTTA CCGCCCGCGT GTCGAACCCA
 AGGCCGGCAG GCGGCACTAG GTACGCCAAT GGCGGGCGCA CAGCTTGGGT
 11301 GGTGTGCGAC GTCAGACAAC GGGGGAGTGC TCCTTTTGGC TTCCTTCCAG
 CCACACGCTG CAGTCTGTTG CCCCCTCACG AGGAAAACCG AAGGAAGGTC

Figure 26L

11401 AAGCGGTTAG GCTGGAAAGC GAAAGCATTAG AGTGGCTCGC TCCCTGTAGC
TTCGCCAATC CGACCTTTTCG CTTTCGTAAT TCACCGAGCG AGGGACATCG

11451 CGGAGGGTTA TTTTCCAAGG GTTGAGTCGC GGGACCCCCG GTTCGAGTCT
GCCTCCCAAT AAAAGGTTCC CAACTCAGCG CCCTGGGGGC CAAGCTCAGA

11501 CGGACCGGCC GGAATGCGGC GAACGGGGGT TTGCCTCCCC GTCATGCAAG
GCCTGGCCGG CCTGACGCCG CTTGCCCCCA AACGGAGGGG CAGTACGTTT

11551 ACCCCGCTTG CAAATTCTTC CGGAAACAGG GACGAGCCCC TTTTGTGCTT
TGGGGCGAAC GTTTAAGGAG GCCTTTGTCC CTGCTCGGGG AAAAAACGAA

11601 TTCCAGATG CATCCGGTGC TGCAGCAGAT GCGCCCCCTT CCTCAGCAGC
AAGGGTCTAC GTAGGCCACG ACGCCGTCTA CGCGGGGGGA GGAGTCGTGC

11651 GGCAAGAGCA AGAGCAGCGG CAGACATGCA GGGCACCTTC CCCTCTCTCT
CCGTCTCTGT TCTCGTCGCC GTCTGTACGT CCCGTGGGAG GGGAGGAGGA

11701 ACCGCGTCAG GAGGGGCGAC ATCCGCGGTT GACGCGGCAG CAGATGGTGA
TGGCGCAGTC CTCCCCGTG TAGGCGCCAA CTGCGCCGTC GTCTACCACT

11751 TTACGAACCC CCGCGGCGCC GGGCCCGGCA CTACCTGGAC TTGGAGGAGG
AATGCTTGGG GGCGCCGCGG CCCGGGCGGT GATGGACCTG AACCTCTCTC

11801 GCGAGGGCCT GGCGCGGCTA GGAGCGCCCT CTCCTGAGCG GCACCCAAGG
CGCTCCCGGA CCGCGCCGAT CCTCGCGGGA GAGGACTCGC CGTGGGTTCC

11851 GTGCAGCTGA AGCGTGATAC GCGTGAGGCG TACGTGCCGC GGCAGAACCT
CACGTCGACT TCGCACTATG CGCACTCCGC ATGCACGGCG CCGTCTTGGA

11901 GTTTCGCGAC CCGGAGGGAG AGGAGCCCGA GGAGATGCGG GATCGAAAGT
CAAAGCGCTG GCGCTCCCTC TCCTCGGGCT CCTCTACGCC CTAGCTTTCA

11951 TCCACGCAGG GCGCGAGCTG CGGCATGGCC TGAATCGCGA GCGGTTGCTG
AGGTGCGTCC CCGCTCGAC GCCGTACCGG ACTTAGCGCT CGCCAACGAC

12001 CGCGAGGAGG ACTTTGAGCC CGACGCGCGA ACCGGGATTA GTCCCGCGCG
GCGCTCCTCC TGAAACTCGG GCTGCGCGCT TGGCCCTAAT CAGGGCGCGC

12051 CGCACACGTG GCGGCCGCGG ACCTGGTAAC CGCATAAGAG CAGACGGTGA
GCGTGTGAC CCGCGGCGGC TGGACCATG GCGTATGCTC GTCTGCCACT

12101 ACCAGGAGAT TAACTTTCAA AAAAGCTTTA ACAACCACGT GCGTACGCTT
TGGTCTCTA ATTGAAAGTT TTTTCGAAAT TGTTGGTGCA CGCATGCGAA

12151 GTGGCGCGCG AGGAGGTGGC TATAGGACTG ATGCATCTGT GGGACTTTGT
CACCGCGCGC TCCTCCACCG ATATCTGAC TACGTAGACA CCCTGAAACA

12201 AAGCGCGCTG GAGCAAAACC CAAATAGCAA GCCGCTCATG GCGCAGCTGT
TTCGCGCGAC CTCGTTTGG GTTTATCGTT CGGCGAGTAC CGCGTCGACA

12251 TCCTTATAGT GCAGCACAGC AGGGACAACG AGGCATTAG GGATGCGCTG
AGGAATATCA CGTCGTGTCG TCCCTGTTGC TCCGTAAGTC CCTACGCGAC

Figure 26 M

12351 CCTGCAGAGC ATAGTGGTGC AGGAGCGCAG CTTGAGCCTG GCTGACAAGG
GGACGTCTCG TATCACCACG TCCTCGCGTC GAACTCGGAC CGACTGTTCC

12401 TGGCCGCCAT CAACTATTCC ATGCTTAGCC TGGGCAAGTT TTACGCCCGC
ACCGCGGTA GTTGATAAGG TACGAATCGG ACCCGTTCAA AATGCGGGCG

12451 AAGATATACC ATACCCCTTA CGTTCCCATG GACAAGGAGG TAAAGATCGA
TTCTATATGG TATGGGGAAT GCAAGGGTAT CTGTTCTCTC ATTTCTAGCT

12501 GGGGTTCTAC ATGCGCATGG CGCTGAAGGT GCTTACCTTG AGCGACGACC
CCCCAAGATG TACGCGTACC GCGACTTCCA CGAATGGAAC TCGCTGCTGG

12551 TGGGCGTTTA TCGCAACGAG CGCATCCACA AGGCCGTGAG CGTGAGCCGG
ACCCGCAAAT AGCGTTGCTC GCGTAGGTGT TCCGGCACTC GCACTCGGCC

12601 CGGCGCGAGC TCAGCGACCG CGAGCTGATG CACAGCCTGC AAAGGGCCCT
GCCGCGCTCG AGTCGCTGGC GCTCGACTAC GTGTCGGACG TTCCCGGGA

12651 GGCTGGCAGC GGCAGCGGCG ATAGAGAGGC CGAGTCCTAC TTTGACGCGG
CCGACCGTGC CCGTCGCCGC TATCTCTCCG GCTCAGGATG AAATGCGCC

12701 GCGCTGACCT GCGCTGGGCC CCAAGCCGAC GCGCCCTGGA GGCAGCTGGG
CGCGACTGGA CGCGACCCGG GGTTCGGCTG CGCGGGACCT CCGTCGACCC

12751 GCCGGACCTG GGCTGGCGGT GGCACCCGCG CGCGCTGGCA ACGTCGGCGG
CGGCCGTGAC CCGACCGCCA CCGTGGGCGC GCGCGACCGT TGCAGCCGCC

12801 CGTGGAGGAA TATGACGAGG ACGATGAGTA CGAGCCAGAG GACGCGGAGT
GCACCTCCTT ATACTGCTCC TGCTACTCAT GCTCGGTCTC CTGCCGCTCA

12851 ACTAAGCGGT GATGTTTCTG ATCAGATGAT GCAAGACGCA ACGGACCCGG
TGATTGCCCA CTACAAAGAC TAGTCTACTA CGTTCTGCGT TGCCTGGGCC

12901 CGGTGCGGGC GGCCTGCAG AGCCAGCCGT CCGGCCTTAA CTCCACGGAC
GCCACGCCCG CCGCGACGTC TCGGTCGGCA GGCCGGAATT GAGGTGCCTG

12951 GACTGGCGCC AGGTCATGGA CCGCATCATG TCGCTGACTG CGCGCAATCC
CTGACCGCGG TCCAGTACCT GCGGTAGTAC AGCGACTGAC GCGCGTTAGG

13001 TGACGCGTTC CCGCAGCAGC CGCAGGCCAA CCGGCTCTCC GCAATTCTGG
ACTGCGCAAG GCCGTCGTCG GCGTCCGGTT GGCCGAGAGG CGTTAAGACC

13051 AAGCGGTGGT CCCGGCGCGC GCAAACCCCA CGCAGAGAA GGTGCTGGCG
TTCGCCACCA GGGCCGCGCG CGTTTGGGGT GCGTGCTCTT CCACGACCGC

13101 ATCGTAAACG CGCTGGCCGA AAACAGGGCC ATCCGGCCCG ACGAGGCCGG
TAGCATTTGC GCGACCGGCT TTTGTCCCGG TAGGCCGGGC TGCTCCGGCC

13151 CCTGGTCTAC GACGCGCTGC TTCAGCGCGT GGCTCGTTAC AACAGCGGCA
GGACCAGATG CTGCGCGACG AAGTCGCGCA CCGAGCAATG TTGTCGCCGT

13201 ACGTGCAAGC CAACCTGGAC CGGCTGGTGG GGGATGTGCG CGAGGCCGTG
TGCACGTCTG GTTGACCTG GCCGACCACC CCCTACACGC GCTCCGGCAC

Figure 26 N

13301 ACTAAACGCC TTCCTGAGTA CACAGCCCGC CAACGTGCCG CGGGGACAGG
TGATTTGCGG AAGGACTCAT GTGTCGGGCG GTTGACCGC GCCCTGTCC

13351 AGGACTACAC CAACTTTGTG AGCGCACTGC GGCTAATGGT GACTGAGACA
TCCTGATGTG GTTGAAACAC TCGCGTGACG CCGATTACCA CTGACTCTGT

13401 CCGCAAAGTG AGGTGTACCA GTCTGGGCCA GACTATTTT TCCAGACCAG
GGCGTTTCAC TCCACATGGT CAGACCCGGT CTGATAAAAA AGGTC'TGGTC

13451 TAGACAAGGC CTGCAGACCG TAAACCTGAG CCAGGCTTTC AAAA'ACTGTC
ATCTGTTCCG GACGTCTGGC ATTTGGACTC GGTCCGAAAG TTTT'TGAACG

13501 AGGGGCTGTG GGGG'TGCGG GCTCCACAG GCGACCGCGC GACCGTGTCT
TCCCCGACAC CCCCCACGCC CGAGGGTGTG CGCTGGCGCG CTGGCACAGA

13551 AGCTTGCTGA CGCCAACTC GCGCCTGTTG CTGCTGCTAA TAGCGCCCTT
TCGAACGACT GCGGGTTGAG CGCGGACAAC GACGACGATT ATCGCGGGAA

13601 CACGGACAGT GGCAGCGTGT CCCGGGACAC ATACCTAGGT CACTTGCTGA
GTGCC'TGTCA CCGTCGCACA GGGCCCTGTG TATGGATCCA GTGAACGACT

13651 CACTGTACCG CGAGGCCATA GGT'CAGGCGC ATGTGGACGA GCATACTTTC
GTGACATGGC GCTCCGGTAT CCAGTCCGCG TACACCTGCT CGTATGAAAG

13701 CAGGAGATTA CAAGTGT'CA GCGCGCGCTG GGGCAGGAGG ACACGGGCAG
GTCTCTAAT GTTACAGTC GCGCGCGGAC CCCGTCTCC TGTGCCCGTC

13751 CCTGGAGGCA ACCCTAAACT ACCTGCTGAC CAACCGGCGG CAGAAGATCC
GGACCTCCGT TGGGATTGTA TGGACGACTG GTTGGCCGCC GTCTTCTAGG

13801 CCTCGTTGCA CAGTTTAAAC AGCGAGGAGG AGCGCATTTT GCGCTACGTG
GGAGCAACGT GTCAAATTTG TCGCTCCTCC TCGCGTAAAA CGCGATGCAC

13851 CAGCAGAGCG TGAGCCTTAA CCTGATGCGC GACGGGGTAA CGCCAGCGT
GTGCTCTCGC ACTCGGAATT GGA'CTACCG CTGCCCCATT GCGGGTGC'CA

13901 GCGCGTGGAC ATGACCGCGC GCAACATGGA ACCGGGCATG TATGCCTCAA
CCGCGACCTG TACTGGCGCG CGTTGTACCT TGGCCCGTAC ATACGGAGTT

13951 ACCGGCCGTT TATCAACCGC CTAATGGACT ACTTGCATCG CGCGGCCGCC
TGGCCGGCAA ATAGTTGGCG GATTACCTGA TGAACGTAGC GCGCCGGCGG

14001 GTGAACCCCG AGTATTT'CA CAATGCCATC TTGAACCCGC ACTGGCTACC
CACTTGGGGC TCATAAAGTG GTTACGGTAG AACTTGGGCG TGACCGATGG

14051 GCCCCCTGGT TTCTACACCG GGGGATTGGA GGTGCCCGAG GGTAACGATG
CGGGGGACCA AAGATGTGGC CCCCTAAGCT CCACGGGCTC CCATTGCTAC

14101 GATTCTCTG GGACGACATA GACGACAGCG TGTTTTCCCC GCAACCGCAG
CTAAGGAGAC CCTGCTGTAT CTGCTGTCGC ACAAAGGGG CGTTGGCGTC

14151 ACCCTGCTAG AGTTGCAACA GCGCGAGCAG GCAGAGGCGG CGCTGCGAAA
TGGGACGATC TCAACGTTGT CCGCTCGTC CGTCTCCGCC GCGACGCTTT

Figure 260

14251 CGCGGTCAGA TGCTAGTAGC CCATTTCCAA GCTTGATAGG GTCTCTTACC
GCGCCAGTCT ACGATCATCG GGTAAAGGTT CGAACTATCC CAGAGAATGG

14301 AGCACTCGCA CCACCCGCCC GCGCCTGCTG GCGGAGGAGG AGTACCTAAA
TCGTGAGCGT GGTGGGCGGG CCGGACGAC CCGCTCCTCC TCATGGATTT

14351 CAACTCGCTG CTGCAGCCGC AGCGCGAAAA AAACCTGCCT CCGGCATTTT
GTTGAGCGAC GACGTCGGCG TCGCGCTTTT TTTGGACGGA GGCCGTAAAG

14401 CCAACAACGG GATAGAGAGC CTAGTGGACA AGATGAGTAG ATGGAAGACG
GGTTGTTGCC CTATCTCTCG GATCACCTGT TCTACTCATC TACCTTCTGC

14451 TACGCGCAGG AGCACAGGGA CGTGCCAGGC CCGCGCCCGC CCACCCGTCG
ATGCGCGTCC TCGTGTCCCT GCACGGTCCG GCGCGGGGCG GGTGGGCAGC

14501 TCAAAGGCAC GACCGTCAGC GGGGTCTGGT GTGGGAGGAC GATGACTCGG
AGTTTCCGTG CTGGCAGTCG CCCAGACCA CACCCTCCTG CTACTGAGCC

14551 CAGACGACAG CAGCGTCCTG GATTGGGAG GGAGTGGCAA CCCGTTTGCG
GTCTGCTGTC GTCGCAGGAC CTAAACCTC CCTCACCGTT GGGCAAACGC

14601 CACCTTCGCC CCAGGCTGGG GAGAATGTTT TAAAAAATAA AAAAGCATGA
GTGGAAGCGG GGTCCGACCC CTCTTACAAA ATTTTTTTTT TTTTCGTACT

14651 TGCAAAATAA AAAACTCACC AAGGCCATGG CACCGAGCGT TGGTTTTCTT
ACGTTTTATT TTTTGAGTGG TTCCGGTACC GTGGCTCGCA ACCAAAAGAA

14701 GTATTCCCTT TAGTATGCGG CGCGCGGCGA TGTATGAGGA AGGTCTCTCT
CATAAGGGGA ATCATACGCC GCGCGCCGCT ACATACTCCT TCCAGGAGGA

14751 CCCTCCTACG AGAGTGTGGT GAGCGCGGCG CCAGTGGCGG CGGCGCTGGG
GGGAGGATGC TCTCACACCA CTCGCGCCGC GGTCACCGCC GCCGCGACCC

14801 TTCTCCCTTC GATGCTCCCC TGGACCCGCC GTTTGTGCCT CCGCGGTACC
AAGAGGGAAG CTACGAGGGG ACCTGGGCGG CAAACACGGA GGCGCCATGG

14851 TGCGGCCTAC CGGGGGGAGA AACAGCATCC GTTACTCTGA GTTGGCACCC
ACGCCGGATG GCCCCCTCT TTGTCGTAGG CAATGAGACT CAACCGTGGG

14901 CTATTCGACA CCACCCGTGT GTACCTGGTG GACAACAAGT CAACGGATGT
GATAAGCTGT GGTGGGCACA CATGGACCAC CTGTTGTTCA GTTGCCTACA

14951 GGCATCCCTG AACTACCAGA ACGACCACAG CAACTTTCTG ACCACGGTCA
CCGTAGGGAC TTGATGGTCT TGCTGGTGTC GTTGAAAGAC TGGTGCCAGT

15001 TTCAAAACAA TGACTACAGC CCGGGGGAGG CAAGCACACA GACCATCAAT
AAGTTTTGTT ACTGATGTCT GGCCCCCTCC GTTCGTGTGT CTGGTAGTTA

15051 CTTGACGACC GGTGCGACTG GGGCGGCGAC CTGAAAACCA TCCTGCATAC
GAACTGCTGG CCAGCGTGAC CCCGCCGCTG GACTTTTGGT AGGACGTATG

15101 CAACATGCCA AATGTGAACG AGTTCATGTT TACCAATAAG TTTAAGGGCG
GTTGTACGGT TTACACTTGC TCAAGTACAA ATGGTTATTC AAATTCGCG

Figure 26 P

15151 GGGTGATGGT GTCGCGCTTG CCTACTAAGG ACAATCAGGT GGAGCTGAAA
CCCACTACCA CAGCGCGAAC GGATGATTCC TGTTAGTCCA CCTCGACTTT

15201 TACGAGTGGG TGGAGTTCAC GCTGCCCCGAG GGCAACTACT CCGAGACCAT
ATGCTCACCC ACCTCAAGTG CGACGGGCTC CCGTTGATGA GGCTCTGGTA

15251 GACCATAGAC CTTATGAACA ACGCGATCGT GGAGCACTAC TTGAAAGTGG
CTGGTATCTG GAATACTTGT TCGCTAGCA CCTCGTGATG AACTTTCACC

15301 GCAGACAGAA CGGGGTTCTG GAAAGCGACA TCGGGGTAAA GTTTGACACC
CGTCTGTCTT GCCCAAGAC CTTTCGCTGT AGCCCCATT CAAACTGTGG

15351 CGCAACTTCA GACTGGGGTT TGACCCCGTC ACTGGTCTTG TCATGCCTGG
GCGTTGAAGT CTGACCCCAA ACTGGGGCAG TGACCAGAAC AGTACGGACC

15401 GGTATATACA AACGAAGCCT TCCATCCAGA CATCATTTTG CTGCCAGGAT
CCATATATGT TTGCTTCGGA AGGTAGGTCT GTAGTAAAC GACGGTCCTA

15451 GCGGGGTGGA CTTCACCAC AGCCGCTGA GCAACTTGTT GGGCATCCGC
CGCCCCACCT GAAGTGGGTG TCGGCGGACT CGTTGAACAA CCCGTAGGCG

15501 AAGCGGCAAC CCTTCCAGGA GGGCTTTAGG ATCACCTACG ATGATCTGGA
TTCGCCGTTG GGAAGGTCTT CCCGAAATCC TAGTGGATGC TACTAGACCT

15551 GGGTGGTAAC ATTCCCGCAC TGTGGATGT GGACGCCTAC CAGGCGAGCT
CCCACCATTG TAAGGGCGTG ACAACCTACA CCTGCGGATG GTCCGCTCGA

15601 TGAAAGATGA CACCGAACAG GCGGGGGTG GCGCAGGCGG CAGCAACAGC
ACTTTCTACT GTGGCTTGTC CCGCCCCAC CGCGTCCGCC GTCGTTGTGC

15651 AGTGGCAGCG GCGCGGAAGA GAACTCCAAC GCGGCAGCCG CGGCAATGCA
TCACCGTCGC CGCGCCTTCT CTTGAGGTG CGCCGTCGGC GCCGTTACGT

15701 GCCGGTGGAG GACATGAACG ATCATGCCAT TCGCGGCGAC ACCTTTGCCA
CGGCCACCTC CTGTACTTGC TAGTACGGTA AGCGCCGCTG TGGAAACGGT

15751 CACGGGCTGA GGAGAAGCGC GCTGAGGCCG AAGCAGCGGC CGAAGCTGCC
GTGCCCGACT CCTCTTCGCG CGACTCCGGC TTCGTCGCCG GCTTCGACGG

15801 GCCCCCGCTG CGCAACCCGA GGTCGAGAAG CCTCAGAAGA AACCAGTGAT
CGGGGGCGAC GCGTTGGGCT CCAGCTCTTC GGAGTCTTCT TTGGCCACTA

15851 CAAACCCCTG ACAGAGGACA GCAAGAAACG CAGTTACAAC CTAATAAGCA
GTTTGGGGAC TGTCTCCTGT CGTTCTTTGC GTCAATGTTG GATTATTCTG

15901 ATGACAGCAC CTTCACCAG TACCGCAGCT GGTACCTTGC ATACAACCTAC
TACTGTCTGT GAAGTGGGTC ATGGCGTCGA CCATGGAACG TATGTTGATG

15951 GCGGACCCTC AGACCGGAAT CCGCTCATGG ACCCTGCTTT GCACCTCTGA
CCGCTGGGAG TCTGGCCTTA GCGAGTACC TGGGACGAAA CGTGAGGACT

16001 CGTAACCTGC GGCTCGGAGC AGGTCTACTG GTCGTTGCCA GACATGATGC
GCATTGGACG CCGAGCCTCG TCCAGATGAC CAGCAACGGT CTGTACTACG

16051 AAGACCCCGT GACCTTCCGC TCCACGCGCC AGATCAGCAA CTTTCCGGTG
TTCTGGGGCA CTGGAAGGCG AGGTGCGCGG TCTAGTCGTT GAAAGGCCAC

Figure 26 A

16151 GGCCGTCTAC TCCCAACTCA TCCGCCAGTT TACCTCTCTG ACCCACGTGT
 CCGGCAGATG AGGGTTGAGT AGGCGGTCAA ATGGAGAGAC TGGGTGCACA
 16201 TCAATCGCTT TCCCGAGAAC CAGATTTTGG CGCGCCCGCC AGCCCCCACC
 AGTTAGCGAA AGGGCTCTTG GTCTAAAACC GCGCGGGCGG TCGGGGGTGG
 16251 ATCACCACCG TCAGTGAAAA CGTTCCTGCT CTCACAGATC ACGGGACGCT
 TAGTGGTGGC AGTCACTTTT GCAAGGACGA GAGTGTCTAG TGCCCTGCGA
 16301 ACCGCTGCGC AACAGCATCG GAGGAGTCCA GCGAGTGACC ATTACTGACG
 TGGCGACGCG TTGTCGTAGC CTCCTCAGGT CGCTCACTGG TAATGACTGC
 16351 CCAGACGCCG CACCTGCCCC TACGTTTACA AGGCCCTGGG CATAGTCTCG
 GGTCTGCGGC GTGGACGGGG ATGCAAATGT TCCGGGACCC GTATCAGAGC
 16401 CCGCGCGTCC TATCGAGCCG CACTTTTTGA GCAAGCATGT CCATCCTTAT
 GCGCGCAGG ATAGCTCGGC GTGAAAACT CGTTCGTACA GGTAGGAATA
 16451 ATCGCCACAG AATAACACAG GCTGGGGCCT GCGCTTCCCA AGCAAGATGT
 TAGCGGGTCG TTATTGTGTC CGACCCCGGA CGCGAAGGGT TCGTTCTACA
 16501 TTGGCGGGGC CAAGAAGCGC TCCGACCAAC ACCCAGTGCG CGTGCGCGGG
 AACC GCCCGG GTTCTTCGCG AGGCTGGTTG TGGGTACGCG GCACGCGCCC
 16551 CACTACCGCG CGCCCTGGGG CGCGCACAAA CGCGGCCGCA CTGGGCGCAC
 GTGATGGCGC GCGGGACCCC GCGCGTGTTT GCGCCGGCGT GACCCGCGTG
 16601 CACCGTCGAT GACGCCATCG ACGCGGTGGT GGAGGAGGCG CGCAACTACA
 GTGGCAGCTA CTGCGGTAGC TGCGCCACCA CCTCCTCCGC GCGTTGATGT
 16651 CGCCACGCC GCCACAGTG TCCACAGTGG ACGCGGCCAT TCAGACCGTG
 GCGGGTGCGG CGGTGGTCAC AGGTGTCACC TGCGCCGGTA AGTCTGGCAC
 16701 GTGCGCGGAG CCCGGCGCTA TGCTAAAATG AAGAGACGGC GGAGGCGCGT
 CACGCGCCTC GGGCCGCGAT ACGATTTTAC TTCTCTGCCG CCTCCGCGCA
 16751 AGCACGTCGC CACCGCCGCC GACCCGGCAC TGCCGCCCAA CGCGCGGCGG
 TCGTGCAGCG GTGGCGGCGG CTGGGCCGTG ACGGCGGGTT GCGCGCCGCC
 16801 CGGCCCTGCT TAACCGCGCA CGTCGCACCG GCCGACGGGC GGCCATGCGG
 GCCGGGACGA ATTGGCGCGT GCAGCGTGGC CGGCTGCCCG CCGGTACGCC
 16851 GCCGCTCGAA GGCTGGCCGC GGGTATTGTC ACTGTGCCCC CCAGGTCCAG
 CGCGGAGCTT CCGACCGGCG CCCATAACAG TGACACGGGG GGTCCAGGTC
 16901 GCGACGAGCG GCCGCCGAG CAGCCGCGGC CATTAGTGCT ATGACTCAGG
 CGCTGCTCGC CGGCGGCGTC GTCGGCGCCG GTAATCACGA TACTGAGTCC
 16951 GTCGCAGGGG CAACGTGTAT TGGGTGCGCG ACTCGGTTAG CGGCCTGCGC
 CAGCGTCCCC GTTGCACATA ACCCAGCGCG TGAGCCAATC GCCGGACGCG
 17001 GTGCCCCTGC GCACCCGCCC CCCGCGCAAC TAGATTGCAA GAAAAAATA
 CACGGGCACG CGTGGGCGGG GGGCGCGTTG ATCTAACGTT CTTTTTTGAT

Figure 26 R

17101 CTATGTCCAA GCGCAAAATC AAAGAAGAGA TGCTCCAGGT CATCGCGCCG
 GATACAGGTT CGCGTTTTAG TTTCTTCTCT ACGAGGTCCA GTAGCGCGGC

17151 GAGATCTATG GCGGGGCGAA GAAGGAAGAG CAGGATTACA AGCCCCGAAA
 CTCTAGATAC CGGGGGGCTT CTTCTTCTCT GTCCTAATGT TCGGGGCTTT

17201 GCTAAAGCGG GTCAAAAAGA AAAAGAAAGA TGATGATGAT GAACTTGACG
 CGATTTTCGCC CAGTTTTTCT TTTTCTTTCT ACTACTACTA CTTGAACTGC

17251 ACGAGGTGGA ACTGCTGCAC GCTACCGCGC CCAGGCGACG GGTACAGTGG
 TGCTCCACCT TGACGACGTG CGATGGCGCG GGTCCGCTGC CCATGTCACC

17301 AAAGGTTCGAC GCGTAAACG TGTTTTGCGA CCCGGCACCA CCGTAGTCTT
 TTTCCAGCTG CGCATTTTGC ACAAACGCT GGGCCGTGGT GGCATCAGAA

17351 TACGCCCCGT GAGCGCTCCA CCCGCACCTA CAAGCGCGTG TATGATGAGG
 ATGCGGGCCA CTCGCGAGGT GGGCGTGGAT GTTCGCGCAC ATACTACTCC

17401 TGTACGGCGA CGAGGACCTG CTTGAGCAGG CCAACGAGCG CCTCGGGGAG
 ACATGCCGCT GTCCTGGAC GAACTCGTCC GGTGCTCGC GGAGCCCCCTC

17451 TTTGCCTACG GAAAGCGGCA TAAGGACATG CTGGCGTTGC CGCTGGACGA
 AAACGGATGC CTTTCGCCGT ATTCTGTAC GACCGCAACG GCGACCTGCT

17501 GGGCAACCCA ACACCTAGCC TAAAGCCCGT AACACTGCAG CAGGTGCTGC
 CCCGTTGGGT TGTGGATCGG ATTTCCGGCA TTGTGACGTC GTCCACGACG

17551 CCGCGCTTGC ACCGTCCGAA GAAAAGCGCG GCCTAAAGCG CGAGTCTGGT
 GGGCGGAACG TGGCAGGCTT CTTTTCGCGC CGGATTTCCG GCTCAGACCA

17601 GACTTGCGAC CCACCGTGCA GCTGATGGTA CCCAAGCGCC AGCGACTGGA
 CTGAACCGTG GGTGGCACGT CGACTACCAT GGGTTCGCGG TCGCTGACCT

17651 AGATGTCTTG GAAAAATGA CCGTGGAACC TGGGCTGGAG CCCGAGGTCC
 TCTACAGAAC CTTTTTTACT GGCACCTTGG ACCCGACCTC GGGCTCCAGG

17701 GCGTGCGGCC AATCAAGCAG GTGGCGCCGG GACTGGGCGT GCAGACCGTG
 CGCACGCCGG TTAGTTCGTC CACCGCGGCC CTGACCCGCA CGTCTGGCAC

17751 GACGTTTCTG TACCCACTAC CAGTAGCACC AGTATTGCCA CCGCCACAGA
 CTGCAAGTCT ATGGGTGATG GTCATCGTGG TCATAACGGT GGCGGTGTCT

17801 GGGCATGGAG ACACAAACGT CCCCGGTTGC CTCAGCGGTG GCGGATGCCG
 CCCGTACCTC TGTGTTTGCA GGGGCCAACG GAGTCGCCAC CGCCTACGGC

17851 CGGTGCAGGC GGTGCTGCGG GCGCGTCCA AGACCTCTAC GGAGGTGCAA
 GCCACGTCCG CCAGCGACGC CGGCGCAGGT TCTGGAGATG CCTCCACGTT

17901 ACGGACCCGT GGATGTTTCG CGTTTCAGCC CCGGCGCGCC CGCGCCGTTT
 TGCCTGGGCA CCTACAAAGC GCAAAGTCGG GGGGCCGCGG GCGCGGCAAG

17951 GAGGAAGTAC GCGCGCGCCA GCGCGCTACT GCGCGAATAT GCCCTACATC
 CTCCTTCATG CCGCGGCGGT CGCGCGATGA CGGGCTTATA CGGGATGTAG

Figure 26S

18051 AGACGAGCAA CTACCCGACG CCGAACCACC ACTGGAACCC GCCGCCGCCG
TCTGCTCGTT GATGGGCTGC GGCTTGGTGG TGACCTTGGG CGGCGGCGGC

18101 TCGCCGTCGC CAGCCCGTGC TGGCCCCGAT TTCCGTGCGC AGGGTGGCTC
AGCGGCAGCG GTCGGGCACG ACCGGGGCTA AAGGCACGCG TCCCACCGAG

18151 GCGAAGGAGG CAGGACCCTG GTGCTGCCAA CAGCGCGCTA CCACCCAGC
CGCTTCCTCC GTCTGGGAC CACGACGGTT GTCGCGCGAT GGTGGGGTCG

18201 ATCGTTTAAA AGCCGGTCTT TGTGGTTCTT GCAGATATGG CCCTCACCTG
TAGCAAATTT TCGGCCAGAA ACACCAAGAA CGTCTATACC GGGAGTGGAC

18251 CCGCCTCCGT TTCCCGGTGC CGGGATTCCG AGGAAGAATG CACCGTAGGA
GGCGGAGGCA AAGGGCCACG GCCCTAAGGC TCCTTCTTAC GTGGCATCCT

18301 GGGGCATGGC CGGCCACGGC CTGACGGGCG GCATGCGTCG TCGCGACCAC
CCCCGTACCG GCCGGTGCCG GACTGCCCGC CGTACGCAGC ACGCGTGGTG

18351 CGGCGGCGGC GCGCGTCGCA CCGTCGCATG CGCGGCGGTA TCCTGCCCCT
GCCGCCGCCG CCGCGACGCT GGCAGCGTAC GCGCCGCCAT AGGACGGGGA

18401 CCTTATTCCA CTGATCGCCG CGGCGATTGG CGCCGTGCCC GGAATTGCAT
GGAATAAGGT GACTAGCGGC GCCGCTAACC GCGGCACGGG CCTTAACGTA

18451 CCGTGGCCTT GCAGGCGCAG AGACACTGAT TAAAAACAAG TTGCATGTGG
GGCACC GGAA CGTCCGCGTC TCTGTGACTA ATTTTGTTC AACGTACACC

18501 AAAAATCAAA ATAAAAAGTC TGGACTCTCA CGCTCGCTTG GTCCTGTAAC
TTTTTAGTTT TATTTTTCAG ACCTGAGAGT GCGAGCGAAC CAGGACATTG

18551 TATTITGTAG AATGGAAGAC ATCAACTTTG CGTCTCTGGC CCCGCGACAC
ATAAAACATC TTACCTTCTG TAGTTGAAAC GCAGAGACCG GGGCGCTGTG

18601 GGCTCGCGCC CGTTCATGGG AACTGGCAA GATATCGGCA CCAGCAATAT
CCGAGCGCGG GCAAGTACCC TTTGACCGTT CTATAGCCGT GGTGCTTATA

18651 GAGCGGTGGC GCCTTCAGCT GGGGCTCGCT GTGGAGCGGC ATTAAAAATT
CTCGCCACCG CGGAAGTCGA CCCCAGCGA CACCTCGCCG TAATTTTAA

18701 TCGGTTCCAC CGTTAAGAAC TATGGCAGCA AGGCCTGGAA CAGCAGCACA
AGCCAAGGTG GCAATTCTTG ATACCGTCGT TCCGACCTT GTCGTGCTGT

18751 GGCCAGATGC TGAGGGATAA GTTGAAAGAG CAAAATTTC AACAAAAGGT
CCGGTCTACG ACTCCCTATT CAACTTTCTC GTTTTAAAGG TTGTTTCCA

18801 GGTAGATGGC CTGGCCTCTG GCATTAGCGG GGTGGTGGAC CTGGCCAACC
CCATCTACCG GACCGGAGAC CGTAATCGCC CCACCACCTG GACCGGTGG

18851 AGGCAGTGCA AAATAAGATT AACAGTAAGC TTGATCCCCG CCCTCCCGTA
TCCGTCACGT TTTATTCTAA TTGTCATTCT AACTAGGGGC GGGAGGGCAT

18901 GAGGAGCCTC CACCGGCCGT GGAGACAGTG TCTCCAGAGG GGCGTGGCGA
CTCCTCGGAG GTGGCCGGCA CCTCTGTCAC AGAGGTCTCC CCGCACCGCT

Figure 26 T

19001 AGCCTCCCTC GTACGAGGAG GCACTAAAGC AAGGCCTGCC CACCACCCGT
 TCGGAGGGAG CATGCTCCTC CGTGATTTCG TTCCGGACGG GTGGTGGGCA
 19051 CCCATCGCGC CCATGGCTAC CGGAGTGCTG GGCCAGCACA CACCCGTAAC
 GGGTAGCGCG GGTACCGATG GCCTCACGAC CCGGTCGTGT GTGGGCATTG
 19101 GCTGGACCTG CCTCCCCCG CCGACACCCA GCAGAAACCT GTGCTGCCAG
 CGACCTGGAC GGAGGGGGGC GGCTGTGGGT CGTCTTTGGA CACGACGGTC
 19151 GCCCCACCGC CGTTGTTGTA ACCCGTCCTA GCCGCGCGTC CCTGCGCCGC
 CGGGCTGGCG GCAACAACAT TGGGCAGGAT CGGCGCGCAG GGACGCGGCG
 19201 GCCGCCAGCG GTCCGCGATC GTTGCGGCCC GTAGCCAGTG GCAACTGGCA
 CGGCGGTGCG CAGGCGCTAG CAACCCCGGG CATCGGTAC CGTTGACCGT
 19251 AAGCACACTG AACAGCATCG TGGGTCTGGG GGTGCAATCC CTGAAGCGCC
 TTCGTGTGAC TTGTCTGATG ACCCAGACCC CCACGTTAGG GACTTCGCGG
 19301 GACGATGCTT CTGATAGCTA ACGTGTCGTA TGTGTGTCAT GTATGCGTCC
 CTGCTACGAA GACTATCGAT TGCACAGCAT ACACACAGTA CATACGCAGG
 19351 ATGTCGCCGC CAGAGGAGCT GCTGAGCCGC CGCGCGCCCG CTTTCCAAGA
 TACAGCGGCG GTCTCCTCGA CGACTCGGCG GCGCGCGGGC GAAAGGTTCT
 19401 TGGCTACCCC TTCGATGATG CCGCAGTGGT CTTACATGCA CATCTCGGGC
 ACCGATGGGG AAGCTACTAC GGCCTCACCA GAATGTACGT GTAGAGCCCG
 19451 CAGGACGCCT CGGAGTACCT GAGCCCCGGG CTGGTGCACT TTGCCCCGCG
 GTCCTGCGGA GCCTCATGGA CTCGGGGCCC GACCACGTCA AACGGGCGCG
 19501 CACCGAGACG TACTTCAGCC TGAATAACAA GTTTAGAAAC CCCACGGTGG
 GTGGCTCTGC ATGAAGTCGG ACTTATTGTT CAAATCTTTG GGGTGCCACC
 19551 CGCCTACGCA CGACGTGACC ACAGACCGGT CCCAGCGTTT GACGCTGCGG
 GCGGATGCGT GCTGCACTGG TGTCTGGCCA GGGTCGCAA CTGEGACGCC
 19601 TTCATCCCTG TGGACCGTGA GGATACTGCG TACTCGTACA AGGCGCGGTT
 AAGTAGGGAC ACCTGGCACT CCTATGACGC ATGAGCATGT TCCGCGCCAA
 19651 CACCCTAGCT GTGGGTGATA ACCGTGTGCT GGACATGGCT TCCACGTACT
 GTGGGATCGA CACCCACTAT TGGCACACGA CCTGTACCGA AGGTGCATGA
 19701 TTGACATCCG CGGCGTGCTG GACAGGGGCC CTACTTTTAA GCCCTACTCT
 AACTGTAGGC GCCGCACGAC CTGTCCCCGG GATGAAAATT CGGGATGAGA
 19751 GGCACCTGCCT ACAACGCCCT GGCTCCCAAG GGTGCCCCAA ATCCTTGCGA
 CCGTGACGGA TGTTCGGGGA CCGAGGGTTC CCACGGGGTT TAGGAACGCT
 19801 ATGGGATGAA GCTGCTACTG CTCTTGAAAT AAACCTAGAA GAAGAGGACG
 TACCCTACTT CGACGATGAC GAGAACTTTA TTTGGATCTT CTTCTCCTGC
 19851 ATGACAACGA AGACGAAGTA GACGAGCAAG CTGAGCAGCA AAAAATCAG
 TACTGTTGCT TCTGCTTCAT CTGCTCGTTC GACTCGTCGT TTTTGTAGTG

Figure 26 U

19951 TCAAATAGGT GTCGAAGGTC AAACACCTAA ATATGCCGAT AAAACATTTTC
AGTTTATCCA CAGCTTCCAG TTTGTGGATT TATACGGCTA TTTTGTAAAG

20001 AACCTGAACC TCAAATAGGA GAATCTCAGT GGTACGAAAC AGAAATTAAT
TTGGACTTGG AGTTTATCCT CTTAGAGTCA CCATGCTTGT TCTTTAATTA

20051 CATGCAGCTG GGAGAGTCCT AAAAAAGACT ACCCCAATGA AACCATGTTA
GTACGTCGAC CCTCTCAGGA TTTTTTCTGA TGGGGTTACT TTGGTACAAT

20101 CGGTTCATAT GCAAAACCCA CAAATGAAAA TGGAGGGCAA GGCATTCTTG
GCCAAGTATA CGTTTGGGT GTTTACTTTT ACCTCCCGTT CCGTAAGAAC

20151 TAAAGCAACA AAATGGAAAG CTAGAAAGTC AAGTGGAAAT GCAATTTTTTC
ATTCGTTGT TTTACCTTTC GATCTTTCAG TTCACCTTTA CGTTAAAAAG

20201 TCAACTACTG AGGCAGCCGC AGGCAATGGT GATAACTTGA CTCCTAAAGT
AGTTGATGAC TCCGTCGGCG TCCGTTACCA CTATTGAACT GAGGATTTC

20251 GGTATTGTAC AGTGAAGATG TAGATATAGA AACCCAGAC ACTCATATTT
CCATAACATG TCACTTCTAC ATCTATATCT TTGGGGTCTG TGAGTATAAA

20301 CTTACATGCC CACTATTAAG GAAGGTAAC CACGAGAACT AATGGGCCAA
GAATGTACGG GTGATAATTC CTTCCATTGA GTGCTCTTGA TTACCCGGTT

20351 CAATCTATGC CCAACAGGCC TAATTACATT GCTTTTAGGG ACAATTTTAT
GTTAGATACG GGTGTCCGG ATTAATGTAA CGAAAATCCC TGTAAAAATA

20401 TGGTCTAATG TATTACAACA GCACGGGTAA TATGGGTGTT CTGGCGGGCC
ACCAGATTAC ATAATGTTGT CGTGCCCAT TATACCCACAA GACCGCCCGG

20451 AAGCATCGCA GTTGAATGCT GTTGTAGATT TGCAAGACAG AACACAGAG
TTCGTAGCGT CAACTTACGA CAACATCTAA ACGTCTGTG TTTGTGTCTC

20501 CTTTCATACC AGCTTTTGCT TGATTCCATT GGTGATAGAA CCAGGTACTT
GAAAGTATGG TCGAAAACGA ACTAAGGTAA CCACTATCTT GGTCCATGAA

20551 TTCTATGTGG AATCAGGCTG TTGACAGCTA TGATCCAGAT GTTAGAATTA
AAGATACACC TTAGTCCGAC AACTGTGAT ACTAGGTCTA CAATCTTAAT

20601 TTGAAATCA TGGAACGTAA GATGAACCTC CAAATTACTG CTTTCCACTG
AACTTTTAGT ACCTTGACTT CTACTTGAAG GTTTAATGAC GAAAGGTGAC

20651 GGAGGTGTGA TTAATACAGA GACTCTTACC AAGGTAAAAC CTAAACAGG
CCTCCACACT AATTATGTCT CTGAGAATGG TTCCATTTTG GATTTTGTCC

20701 TCAGGAAAAT GGATGGGAAA AAGATGCTAC AGAATTTTCA GATAAAAATG
AGTCCTTTTA CCTACCCTTT TTCTACGATG TCTTAAAAGT CTATTTTAC

20751 AAATAAGAGT TGGAAATAAT TTTGCCATGG AAATCAATCT AAATGCCAAC
TTTATTCTCA ACCTTTATTA AAACGGTACC TTTAGTTAGA TTTACGGTTG

20801 CTGTGGAGAA ATTTCTGTGA CTCCAACATA GCGCTGTATT TGCCCGACAA
GACACCTCTT TAAAGGACAT GAGGTTGTAT CGCGACATAA ACGGGCTGTT

Figure 26 v

20901 ACGACTACAT GAACAAGCGA GTGGTGGCTC CCGGGCTAGT GGACTGCTAC
TGCTGATGTA CTTGTTGCT CACCACCGAG GGCCCGATCA CCTGACGATG

20951 ATTAACCTTG GAGCAGCTG GTCCCTTGAC TATATGGACA ACGTCAACCC
TAATTGGAAC CTCGTGCGAC CAGGGAACTG ATATACCTGT TGCAGTTGGG

21001 ATTTAACCAC CACCGCAATG CTGGCCTGCG CTACCGCTCA ATGTTGCTGG
TAAATTGGTG GTGGCGTTAC GACCGGACGC GATGGCGAGT TACAACGACC

21051 GCAATGGTCG CTATGTGCCC TTCCACATCC AGGTGCCTCA GAAGTTCTTT
CGTTACCAGC GATACACGGG AAGGTGTAGG TCCACGGAGT CTTCAAGAAA

21101 GCCATTAAAA ACCTCCTTCT CCTGCCGGGC TCATACACCT ACGAGTGGAA
CGGTAATTTT TGGAGGAAGA GGACGGCCCG AGTATGTGGA TGCTCACCTT

21151 CTTCAGGAAG GATGTTAACA TGGTTCTGCA GAGCTCCCTA GGAAATGACC
GAAGTCCTTC CTACAATTGT ACCAAGACGT CTCGAGGGAT CCTTTACTGG

21201 TAAGGGTTGA CGGAGCCAGC ATTAAGTTTG ATAGCATTTG CCTTTACGCC
ATTCCCAACT GCCTCGGTCG TAATTCAAAC TATCGTAAAC GGAAATGCGG

21251 ACCTTCTTCC CCATGGCCCA CAACACCGCC TCCACGCTTG AGGCCATGCT
TGGAAGAAGG GGTACCGGGT GTTGTGGCGG AGGTGCGAAC TCCGGTACGA

21301 TAGAAACGAC ACCAACGACC AGTCCTTTAA CGACTATCTC TCCGCCGCCA
ATCTTTGCTG TGGTTGCTGG TCAGGAAATT GCTGATAGAG AGGCGGCGGT

21351 ACATGCTCTA CCCTATACCC GCCAACGCTA CCAACGTGCC CATATCCATC
TGTACGAGAT GGGATATGGG CGGTTGCGAT GGTGTCACGG GTATAGGTAG

21401 CCCTCCCGCA ACTGGGCGGC TTTCCGCGGC TGGGCCTTCA CGCGCCTTAA
GGGAGGGCGT TGACCCGCCG AAAGGCGCCG ACCCGGAAGT GCGCGGAATT

21451 GACTAAGGAA ACCCCATCAC TGGGCTCGGG CTACGACCCT TATTACACCT
CTGATTCCTT TGGGGTAGTG ACCCGAGCCC GATGCTGGGA ATAATGTGGA

21501 ACTCTGGCTC TATACCCTAC CTAGATGGAA CCTTTTACCT CAACCACACC
TGAGACCGAG ATATGGGATG GATCTACCTT GGAAAATGGA GTTGGTGTGG

21551 TTTAAGAAGG TGGCCATTAC CTTTGACTCT TCTGTCAGCT GGCCTGGCAA
AAATTCTTCC ACCGGTAATG GAAACTGAGA AGACAGTCGA CCGGACCGTT

21601 TGACCGCCTG CTTACCCCCA ACGAGTTTGA AATTAAGCGC TCAGTTGACG
ACTGGCGGAC GAATGGGGGT TGCTCAAAC TTAATTCGCG AGTCAACTGC

21651 GGGAGGGTTA CAACGTTGCC CAGTGTAACA TGACCAAAGA CTGGTTCCCTG
CCCTCCCAAT GTTGCAACGG GTCACATTGT ACTGGTTTCT GACCAAGGAC

21701 GTACAAATGC TAGCTAACTA TAACATTGGC TACCAGGGCT TCTATATCCC
CATGTTTACG ATCGATTGAT ATTGTAACCG ATGGTCCCGA AGATATAGGG

21751 AGAGAGCTAC AAGGACCGCA TGTACTCCTT CTTTAGAAAC TTCCAGCCCA
TCTCTCGATG TTCCTGGCGT ACATGAGGAA GAAATCTTTG AAGGTCGGGT

Figure 26 W

21851 GGCATCCTAC ACCAACACAA CAACTCTGGA TTTGTTGGCT ACCTTGCCCC
CCGTAGGATG TGGTTGTGTT GTTGAGACCT AAACAACCGA TGGAACGGGG

21901 CACCATGCGC GAAGGACAGG CCTACCCTGC TAACTTCCCC TATCCGCTTA
GTGGTACGCG CTTCTGTCC GGATGGGACG ATTGAAGGGG ATAGGCGAAT

21951 TAGGCAAGAC CGCAGTTGAC AGCATTACCC AGAAAAAGTT TCTTTGCGAT
ATCCGTTCTG GCGTCAACTG TCGTAATGGG TCTTTTCAA AGAAACGCTA

22001 CGCACCCTTT GCGCATCCC ATTCTCCAGT AACTTTATGT CCATGGGCGC
GCGTGGGAAA CCGCGTAGGG TAAGAGGTCA TTGAAATACA GGTACCCGCG

22051 ACTCACAGAC CTGGGCCAAA ACCTTCTCTA CGCCAACTCC GCCACGCGC
TGAGTGTCTG GACCCGGTTT TGAAGAGAT GCGGTTGAGG CGGGTGCGCG

22101 TAGACATGAC TTTTGAGGTG GATCCCATGG ACGAGCCCAC CCTTCTTTAT
ATCTGTACTG AAAACTCCAC CTAGGGTACC TGCTCGGGTG GGAAGAAATA

22151 GTTTTGTTTG AAGTCTTTGA CGTGGTCCGT GTGCACCAGC CGCACCGCGG
CAAAACAAAC TTCAGAACT GCACCAGGCA CACGTGGTCG GCGTGGCGCC

22201 CGTCATCGAA ACCGTGTACC TGCACACGCC CTTCTCGGCC GGCAACGCCA
GCAGTAGCTT TGGCACATGG ACGCGTGCGG GAAGAGCCGG CCGTTGCGGT

22251 CAACATAAAG AAGCAAGCAA CATCAACAAC AGCTGCCGCC ATGGGCTCCA
GTTGTATTTC TTCGTTGTTT GTAGTTGTTG TCGACGGCGG TACCCGAGGT

22301 GTGAGCAGGA ACTGAAAGCC ATTGTCAAAG ATCTTGGTTG TGGGCCATAT
CACTCGTCCT TGACTTTCGG TAACAGTTTC TAGAACCAAC ACCCGGTATA

22351 TTTTGGGCA CCTATGACAA GCGCTTTCCA GGCTTTGTTT CTCCACACAA
AAAAACCCGT GGATACTGTT CGCGAAAGGT CCGAAACAAA GAGGTGTGTT

22401 GCTCGCCTGC GCCATAGTCA ATACGGCCGG TCGCGAGACT GGGGGCGTAC
CGAGCGGACG CCGTATCAGT TATGCCGGCC AGCGCTCTGA CCCCCGATG

22451 ACTGGATGGC CTTTGCTGG AACC CGCACT CAAAAACATG CTACCTCTTT
TGACCTACCG GAAACGGACC TTGGGCGTGA GTTTTGTAC GATGGAGAAA

22501 GAGCCCTTTG GCTTTTCTGA CCAGCGACTC AAGCAGGTTT ACCAGTTTGA
CTCGGGAAAC CGAAAAGACT GGTGCGTGAG TTCGTCCAAA TGGTCAAAC

22551 GTACGAGTCA CTCCTGCGCC GTAGCGCCAT TGCTTCTTCC CCCGACCGCT
CATGCTCAGT GAGGACGCGG CATCGCGGTA ACGAAGAAGG GGGCTGGCGA

22601 GTATAACGCT GGAAAAGTCC ACCCAAAGCG TACAGGGGCC CAACTCGGCC
CATATTGCGA CCTTTTCAGG TGGGTTTCGC ATGTCCCCGG GTTGAGCCGG

22651 GCCTGTGGAC TATTCTGCTG CATGTTTCTC CACGCCTTTG CCAACTGGCC
CGGACACCTG ATAAGACGAC GTACAAAGAG GTGCGGAAAC GGTGACCCG

22701 CCAAACCTCC ATGGATCACA ACCCCACCAT GAACCTTATT ACCGGGGTAC
GGTTTGAGGG TACCTAGTGT TGGGGTGGTA CTGGAATAA TGGCCCCATG

Figure 26 X

22801 CAGGAACAGC TCTACAGCTT CCTGGAGCGC CACTCGCCCT ACTTCGCGAG
GTCCTTGTCG AGATGTCGAA GGACCTCGCG GTGAGCGGGA TGAAGGCGTC

22851 CCACAGTGCG CAGATTAGGA GCGCCACTTC TTTTGTGTCAC TTGAAAAACA
GGTGTACGCG GTCTAATCCT CGCGGTGAAG AAAAACAGTG AACTTTTTGT

22901 TGTA AAAATA ATGTACTAGA GACACTTTCA ATAAAGGCAA ATGCTTTTAT
ACATTTTAT TACATGATCT CTGTGAAAGT TATTTCCGTT TACGAAAAA

22951 TTGTACACTC TCGGGTGATT ATTTACCCCC ACCCTTGCCG TCTGCGCCGT
AACATGTGAG AGCCCACTAA TAAATGGGGG TGGGAACGGC AGACGCGGCA

23001 TTAAAAATCA AAGGGGTTCT GCCGCGCATC GCTATGCGCC ACTGGCAGGG
AATTTTTAGT TTCCCAAGA CGGCGCGTAG CGATACGCGG TGACCGTCCC

23051 ACACGTTGCG ATACTGGTGT TTAGTGCTCC ACTTAAACTC AGGCACAACC
TGTGCAACGC TATGACCACA AATCACGAGG TGAATTTGAG TCCGTGTTGG

23101 ATCCGCGGCA GCTCGGTGAA GTTTTCACTC CACAGGCTGC GCACCATCAC
TAGGCGCCGT CGAGCCACTT CAAAAGTGAG GTGTCCGACG CGTGGTAGTG

23151 CAACGCGTTT AGCAGGTCGG GCGCCGATAT CTTGAAGTCG CAGTTGGGGC
GTTGCGCAAA TCGTCCAGCC CGCGGCTATA GAACTTCAGC GTCAACCCCG

23201 CTCCGCCCTG CGCGCGCGAG TTGCGATACA CAGGGTTGCA GCACTGGAAC
GAGGCGGGAC GCGCGCGCTC AACGCTATGT GTCCCAACGT CGTGACCTTG

23251 ACTATCAGCG CCGGGTGGTG CACGCTGGCC AGCACGCTCT TGTCGGAGAT
TGATAGTCGC GGCCACCAC GTGCGACCGG TCGTGCGAGA ACAGCCTCTA

23301 CAGATCCGCG TCCAGGTCCT CCGCGTTGCT CAGGGCGAAC GGAGTCAACT
GTCTAGGCGC AGGTCCAGGA GGCGCAACGA GTCCCGCTTG CCTCAGTTGA

23351 TTGGTAGCTG CCTTCCCAA AAGGGCGCGT GCCCAGGCTT TGAGTTGCAC
AACCATCGAC GGAAGGGTTT TTCCCGCGCA CGGGTCCGAA ACTCAACGTG

23401 TCGCACCGTA GTGGCATCAA AAGGTGACCG TGCCCGGTCT GGGCGTTAGG
AGCGTGGCAT CACCGTAGTT TTCCACTGGC ACGGGCCAGA CCCGCAATCC

23451 ATACAGCGCC TGCATAAAAG CCTTGATCTG CTTAAAAGCC ACCTGAGCCT
TATGTGCGGG ACGTATTTTC GGAAC TAGAC GAATTTTCGG TGGACTCGGA

23501 TTGCGCCTTC AGAGAAGAAC ATGCCGCAAG ACTTGCCGGA AAAC TGATTG
AACGCGGAAG TCTCTTCTTG TACGGCGTTC TGAACGGCCT TTTGACTAAC

23551 GCCGGACAGG CCGCGTCGTG CACGAGCAC CTTGCGTCGG TGTGGAGAT
CGGCCTGTCC GGCGCAGCAC GTGCGTCGTG GAACGAGCC ACAACCTCTA

23601 CTGCACCACA TTTCGGCCCC ACCGGTTCTT CACGATCTTG GCCTTGCTAG
GACGTGGTGT AAAGCCGGGG TGGCCAAGAA GTGCTAGAAC CGGAACGATC

23651 ACTGCTCCTT CAGCGCGCGC TGCCCGTTTT CGCTCGTCAC ATCCATTTCA
TGACGAGGAA GTCGCGCGCG ACGGGCAAAA GCGAGCAGTG TAGGTAAAGT

Figure 26Y

23701 ATCACGTGCT CCTTATTTAT CATAATGCTT CCGTGTAGAC ACTTAAGCTC
TAGTGACGCA GGAATAAATA GTATTACGAA GGCACATCTG TGAATTCGAG

23751 GCCTTCGATC TCAGCGCAGC GGTGCAGCCA CAACGCGCAG CCCGTGGGCT
CGGAAGCTAG AGTCGCGTCG CCACGTCGGT GTTGC GCGTC GGGCACCCGA

23801 CGTGATGCTT GTAGGTCACC TCTGCAAACG ACTGCAGGTA CGCCTGCAGG
GCACTACGAA CATCCAGTGG AGACGTTTGC TGACGTCCAT GCGGACGTC

23851 AATCGCCCCA TCATCGTCAC AAAGGTCTTG TTGCTGGTGA AGGTCAGCTG
TTAGCGGGGT AGTAGCAGTG TTTCCAGAAC AACGACCACT TCCAGTCGAG

23901 CAACCCGCGG TGCTCCTCGT TCAGCCAGGT CTTGCATACG GCCGCCAGAG
GTTGGGCGCC ACGAGGAGCA AGTCGGTCCA GAACGTATGC CGGCGGTCTC

23951 CTTCCACTTG GTCAGGCAGT AGTTTGAAGT TCGCCTTTAG ATCGTTATCC
GAAGGTGAAC CAGTCCGTCA TCAAACCTCA AGCGGAAATC TAGCAATAGG

24001 ACGTGGTACT TGTCCATCAG CGCGCGCGCA GCCTCCATGC CCTTCTCCCA
TGCACCATGA ACAGGTAGTC GCGCGCGCGT CGGAGGTACG GGAAGAGGGT

24051 CGCAGACACG ATCGGCACAC TCAGCGGGTT CATCACCGTA ATTTCACTTT
GCGTCTGTGC TAGCCGTGTG AGTCGCCCAA GTAGTGGCAT TAAAGTGAAA

24101 CCGCTTCGCT GGGCTCTTCC TCTTCTCTT GCGTCCGCAT ACCACGCGCC
GGCGAAGCGA CCCGAGAAGG AGAAGGAGAA CGCAGGCGTA TGGTGCGCGG

24151 ACTGGGTCGT CTTCAATCAG CCGCCGCACT GTGCGCTTAC CTCCTTTGCC
TGACCCAGCA GAAGTAAGTC GCGGCGGTGA CACGCGAATG GAGGAAACGG

24201 ATGCTTGATT AGCACCGGTG GGTGCTGAA ACCCACCATT TGTAGCGCCA
TAGGAATAA TCGTGGCCAC CCAACGACTT TGGGTGGTAA ACATCGCGGT

24251 CATCTTCTCT TTCTTCCTCG CTGTCCACGA TTACCTCTGG TGATGGCGGG
GTAGAAGAGA AAGAAGGAGC GACAGGTGCT AATGGAGACC ACTACCGCCC

24301 CGCTCGGGCT TGGGAGAAGG GCGCTTCTTT TTCTTCTTGG GCGCAATGGC
GCGAGCCCGA ACCCTCTTCC CGCGAAGAAA AAGAAGAACC CGCGTTACCG

24351 CAAATCCGCC GCCGAGGTCG ATGGCCGCGG GCTGGGTGTG CGCGGCACCA
GTTTAGGCGG CGGCTCCAGC TACCGGCGCC CGACCCACAC GCGCCGTGGT

24401 GCGCGTCTTG TGATGAGTCT TCCTCGTCCT CGGACTCGAT ACGCCGCCTC
CGCGCAGAAC ACTACTCAGA AGGAGCAGGA GCCTGAGCTA TGCGGCGGAG

24451 ATCCGCTTTT TTGGGGGCGC CCGGGGAGGC GCGGCGGACG GGGACGGGGA
TAGGCGAAAA AACCCTCGCG GGCCCTCCG CCGCCGCTGC CCCTGCCCTT

24501 CGACACGTCC TCCATGGTTG GGGGACGTCG CGCCGCACCG CGTCCGCGCT
GCTGTGCAGG AGGTACCAAC CCCCTGCAGC GCGGCGTGTC GCAGGCGCGA

24551 CGGGGGTGGT TTCGCGCTGC TCCTCTTCCC GACTGGCCAT TTCCTTCTCC
GCCCCACCA AAGCGCGACG AGGAGAAGGG CTGACCGGTA AAGGAAGAGG

24601 TATAGGCAGA AAAAGATCAT GGAGTCAGTC GAGAAGAAGG ACAGCCTAAC
ATATCCGTCT TTTTCTAGTA CCTCAGTCAG CTCTTCTTCC TGTGGGATTG

24701 CTACCACCTT CCCCCTCGAG GCACCCCGC TTGAGGAGGA GGAAGTGATT
 GATGGTGGAA GGGGCAGCTC CGTGGGGGCG AACTCCTCCT CCTTCACTAA
 24751 ATCGAGCAGG ACCCAGGTTT TGTAAAGCGAA GACGACGAGG ACCGCTCAGT
 TAGCTCGTCC TGGGTCCAAA ACATTGCTT CTGCTGCTCC TGGCGAGTCA
 24801 ACCAACAGAG GATAAAAAGC AAGACCAGGA CAACGCAGAG GCAAACGAGG
 TGGTTGTCTC CTATTTTTCG TTCTGGTCCT GTTGCCTCTC CGTTTGCTCC
 24851 AACAAGTCGG GCGGGGGGAC GAAAGGCATG GCGACTACCT AGATGTGGGA
 TTGTTTACGCC CGCCCCCTG CTTTCCGTAC CGCTGATGGA TCTACACCTT
 24901 GACGACGTGC TGTTGAAGCA TCTGCAGCGC CAGTGCGCCA TTATCTGCGA
 CTGCTGCACG ACAACTTCGT AGACGTGCGG GTCACGCGGT AATAGACGCT
 24951 CGCGTTGCAA GAGCGCAGCG ATGTGCCCTT CGCCATAGCG GATGTCAGCC
 GCGCAACGTT CTCGCGTCGC TACACGGGGA GCGGTATCGC CTACAGTCGG
 25001 TTGCCTACGA ACGCCACCTA TTCTCACC GC GTACCCCA CAAACGCCAA
 AACGGATGCT TCGGGTGGAT AAGAGTGGCG CGCATGGGGG GTTTGCGGTT
 25051 GAAAACGGCA CATGCGAGCC CAACCCGCGC CTCAACTTCT ACCCGGTATT
 CTTTGGCCGT GTACGCTCGG GTTGGGCGCG GAGTTGAAGA TGGGGCATAA
 25101 TGCCGTGCCA GAGGTGCTTG CCACCTATCA CATCTTTTTC CAAACTGCA
 ACGGCACGGT CTCCACGAAC GGTGGATAGT GTAGAAAAAG GTTTTGACGT
 25151 AGATACCCCT ATCCTGCCGT GCCAACCACA GCCGAGCGGA CAAGCAGCTG
 TCTATGGGGA TAGGACGGCA CGGTTGGCGT CGGCTCGCCT GTTCGTCGAC
 25201 GCCTTGCGGC AGGGCGCTGT CATACTGAT ATCGCCTCGC TCAACGAAGT
 CGGAACGCCG TCCCGCGACA GTATGGACTA TAGCGGAGCG AGTTGCTTCA
 25251 GCCAAAAATC TTGAGGGTC TTGGACGCGA CGAGAAGCGC GCGGCAAACG
 CGGTTTTTAG AAACCTCCAG AACCTGCGCT GCTCTTCGCG CGCCGTTTGC
 25301 CTCTGCAACA GGAAAACAGC GAAAATGAAA GTCACCTCTG AGTGTGGTG
 GAGACGTTGT CCTTTTGTCT CTTTTACTTT CAGTGAGACC TCACAACCAC
 25351 GAACTCGAGG GTGACAACGC GCGCCTAGCC GTACTAAAAC GCAGCATCGA
 CTTGAGCTCC CACTGTTGCG CGCGGATCGG CATGATTTTG CGTCGTAGCT
 25401 GGTCACCCAC TTTGCCTACC CGGCACCTAA CCTACCCCA AAGGTCATGA
 CCAGTGGGTG AAACGGATGG GCCGTGAATT GGATGGGGGG TTCCAGTACT
 25451 GCACAGTCAT GAGTGAGCTG ATCGTGCGCC GTGCGCAGCC CCTGGAGAGG
 CGTGTCAGTA CTCACTCGAC TAGCACGCGG CACGCGTCGG GGACCTCTCC
 25501 GATGCAAATT TGCAAGAACA AACAGAGGAG GGCCTACCCG CAGTTGGCGA
 CTACGTTTAA ACGTTCTTGT TTGTCTCCTC CCGGATGGGC GTCAACCGCT
 25551 CGAGCAGCTA GCGCGCTGGC TTCAAACGCG CGAGCCTGCC GACTTGGAGG
 GCTCGTCGAT CGCGCGACCG AAGTTTGC GC GCTCGGACGG CTGAACCTCC

Figure 26 AA

25651 TGCATGCAGC GGTTCCTTGC TGACCCGGAG ATGCAGCGCA AGCTAGAGGA
ACGTACGTCG CCAAGAAACG ACTGGGCCTC TACGTCGCGT TCGATCTCCT

25701 AACATTGCAC TACACCTTTC GACAGGGCTA CGTACGCCAG GCCTGCAAGA
TTGTAACGTG ATGTGGAAAG CTGTCCCGAT GCATGCGGTC CGGACGTTCT

25751 TCTCCAACGT GGAGCTCTGC AACCTGGTCT CCTACCTTGG AATTTTGCAC
AGAGGTTGCA CCTCGAGACG TTGGACCAGA GGATGGAACC TTAACACGTG

25801 GAAAACCGCC TTGGGCAAAA CGTGCTTCAT TCCACGCTCA AGGGCGAGGC
CTTTTGGCGG AACCCGTTTT GCACGAAGTA AGGTGCGAGT TCCCGCTCCG

25851 GCGCCGCGAC TACGTCCGCG ACTGCGTTTA CTTATTTCTA TGCTACACCT
CGCGGCGCTG ATGCAGGCGC TGACGCAAAAT GAATAAAGAT ACGATGTGGA

25901 GGCAGACGGC CATGGGCGTT TGGCAGCAGT GCTTGAGGGA GTGCAACCTC
CCGTCTGCCG GTACCCGCAA ACCGTCGTCA CGAACCTCCT CACGTTGGAG

25951 AAGGAGCTGC AGAAACTGCT AAAGCAAAC TTGAAGGACC TATGGACGGC
TTCTTCGACG TCTTTGACGA TTTCGTTTG AACCTCCTGG ATACCTGCCG

26001 CTTCAACGAG CGCTCCGTGG CCGCGCACCT GCGGACATC ATTTTCCCCG
GAAGTTGCTC GCGAGGCACC GCGCGTGGA CCGCTGTAG TAAAAGGGGC

26051 AACGCCTGCT TAAAACCCTG CAACAGGGTC TGCCAGACTT CACCAGTCAA
TTGCGGACGA ATTTTGGGAC GTTGTCCAG ACGGTCTGAA GTGGTCAGTT

26101 AGCATGTTGC AGAACTTTAG GAACTTTATC CTAGAGCGCT CAGGAATCTT
TCGTACAACG TCTTGAAATC CTTGAAATAG GATCTCGCA GTCTTAGAA

26151 GCGCGCCACC TGCTGTGCAC TTCCTAGCGA CTTTGTGCCC ATTAAGTACC
CGGGCGGTGG ACGACACGTG AAGGATCGCT GAAACACGGG TAATTCATGG

26201 GCGAATGCCC TCCGCCGCTT TGGGGCCACT GCTACCTTCT GCAGCTAGCC
CGCTTACGGG AGGCGGCGAA ACCCCGGTGA CGATGGAAGA CGTCGATCGG

26251 AACTACCTTG CCTACCACTC TGACATAATG GAAGACGTGA GCGGTGACGG
TTGATGGAAC GGATGGTGAG ACTGTATTAC CTTCTGCACT CGCCACTGCC

26301 TCTACTGGAG TGCTACTGTC GCTGCAACCT ATGCACCCCG CACCGCTCCC
AGATGACCTC ACGTGACAG CGACGTTGGA TACGTGGGGC GTGGCGAGGG

26351 TGGTTTGCAA TTCGCAGCTG CTTAACGAAA GTCAAATTAT CGGTACCTTT
ACCAAACGTT AAGCGTCGAC GAATTGCTTT CAGTTTAATA GCCATGGAAA

26401 GAGCTGCAGG GTCCCTCGCC TGACGAAAAG TCCGCGGCTC CGGGGTTGAA
CTCGACGTCC CAGGGAGCGG ACTGCTTTTC AGGCGCCGAG GCCCAACTT

26451 ACTCACTCCG GGGCTGTGGA CGTCGGCTTA CCTTCGCAA TTTGTACCTG
TGAGTGAGGC CCCGACACCT GCAGCCGAAT GGAAGCGTTT AACATGGAC

26501 AGGACTACCA CGCCCACGAG ATTAGGTTCT ACGAAGACCA ATCCCGCCCG
TCCTGATGGT GCGGGTGCTC TAATCCAAGA TGCTTCTGGT TAGGGCGGGC

Figure 26 AB

26551 CCTAATGCGG AGCTTACCGC CTGCGTCATT ACCCAGGGCC ACATTCTTGG
GGATTACGCC TCGAATGGCG GACGCAGTAA TGGGTCCCGG TGTAAGAACC

26601 CCAATTGCAA GCCATCAACA AAGCCCGCCA AGAGTTTCTG CTACGAAAGG
GGTTAACGTT CGGTAGTTGT TTCGGGCGGT TCTCAAAGAC GATGCTTTCC

26651 GACGGGGGGT TTACTTGGAC CCCAGTCCG GCGAGGAGCT CAACCCAATC
CTGCCCCCA AATGAACCTG GGGGTCAGGC CGCTCCTCGA GTTGGGTTAG

26701 CCCCCGCCGC CGCAGCCCTA TCAGCAGCAG CCGCGGGCCC TTGCTTCCCA
GGGGGCGGCG GCGTCGGGAT AGTCGTCGTC GCGCCCCGGG AACGAAGGCT

26751 GGATGGCACC CAAAAAGAAG CTGCAGCTGC CGCCGCCACC CACGGACGAG
CCTACCGTGG GTTTTCTTTC GACGTCGACG GCGGCGGTGG GTGCCTGCTC

26801 GAGGAATACT GGGACAGTCA GGCAGAGGAG GTTTTGGACG AGGAGGAGGA
CTCCTTATGA CCCTGTCAGT CCGTCTCCTC CAAAACCTGC TCCTCCTCCT

26851 GGACATGATG GAAGACTGGG AGAGCCTAGA CGAGGAAGCT TCCGAGGTCTG
CCTGTACTAC CTTCTGACCC TCTCGGATCT GCTCCTTCGA AGGCTCCAGC

26901 AAGAGGTGTC AGACGAAACA CCGTCACCCT CGGTGCGATT CCCCTCGCCG
TTCTCCACAG TCTGCTTTGT GGCAGTGGGA GCCAGCGTAA GGGGAGCGGC

26951 GCGCCCCAGA AATCGGCAAC CGGTTCCAGC ATGGCTACAA CCTCCGCTCC
CGCGGGGTCT TTAGCCGTTG GCCAAGGTCG TACCGATGTT GGAGGCGAGG

27001 TCAGGCGCCG CCGGCACTGC CCGTTCGCCG ACCCAACCGT AGATGGGACA
AGTCCGCGGC GGCCGTGACG GGCAAGCGGC TGGGTTGGCA TCTACCCTGT

27051 CCACTGGAAC CAGGGCCGGT AAGTCCAAGC AGCCGCCGCC GTTAGCCCAA
GGTGACCTTG GTCCCGGCCA TTCAGGTTTCG TCGGCGGCGG CAATCGGGTT

27101 GAGCAACAAC AGCGCCAAGG CTACCGCTCA TGGCGCGGGC ACAAGAACGC
CTCGTTGTTG TCGCGGTTCC GATGGCGAGT ACCGCGCCCG TGTTCTTGCG

27151 CATAGTTGCT TGCTTGCAAG ACTGTGGGGG CAACATCTCC TTCGCCCCGC
GTATCAACGA ACGAACGTTT TGACACCCCC GTTGTAGAGG AAGCGGGCGG

27201 GCTTTCTTCT CTACCATCAC GGCGTGGCCT TCCCCCGTAA CATCCTGCAT
CGAAAGAAGA GATGGTAGTG CCGCACCGGA AGGGGGCATT GTAGGACGTA

27251 TACTACCGTC ATCTCTACAG CCCATACTGC ACCGGCGGCA GCGGCAGCAA
ATGATGGCAG TAGAGATGTC GGGTATGACG TGGCCGCCGT CGCCGTCGTT

27301 CAGCAGCGGC CACACAGAAG CAAAGGCGAC CGGATAGCAA GACTCTGACA
GTCGTCGCCG GTGTGTCTTC GTTCCGCTG GCCTATCGTT CTGAGACTGT

27351 AAGCCCAAGA AATCCACAGC GCGGCGAGCA GCAGGAGGAG GAGCGCTGCG
TTCGGGTCTT TTAGGTGTCG CCGCCGTCGT CGTCCTCCTC CTCGCGACGC

27401 TCTGGCGCCC AACGAACCCG TATCGACCCG CGAGCTTAGA AACAGGATTT
AGACCGCGGG TTGCTTGGGC ATAGCTGGGC GCTCGAATCT TTGTCTAAA

27451 TTCCCACTCT GTATGCTATA TTCAACAGA GCAGGGGCCA AGAACAAGAG
AAGGGTGAGA CATACGATAT AAAGTTGTCT CGTCCCCGGT TCTTGTCTC

Figure 26: AC

27551 TCACAAAAGC GAAGATCAGC TTCGGCGCAC GCTGGAAGAC GCGGAGGCTC
AGTGTTTTTCG CTTCTAGTCG AAGCCGCGTG CGACCTTCTG CGCCTCCGAG

27601 TCTTCAGTAA ATACTGCGCG CTGACTCTTA AGGACTAGTT TCGCGCCCTT
AGAAGTCATT TATGACGCGC GACTGAGAAT TCCTGATCAA AGCGCGGGAA

27651 TCTCAAATTT AAGCGCGAAA ACTACGTCAT CTCCAGCGGC CACACCCGGC
AGAGTTTAAA TTCGCGCTTT TGATGCAGTA GAGGTCGCCG GTGTGGGCCG

27701 GCCAGCACCT GTTGTCAGCG CCATTATGAG CAAGGAAATT CCCACGCCCT
CGGTCGTGGA CAACAGTCGC GGTAACTACTC GTTCCTTTAA GGGTGCGGGA

27751 ACATGTGGAG TTACCAGCCA CAAATGGGAC TTGCGGCTGG AGCTGCCCAA
TGTACACCTC AATGGTCGGT GTTTACCCTG AACGCCGACC TCGACGGGTT

27801 GACTACTCAA CCCGAATAAA CTACATGAGC GCGGGACCCC ACATGATATC
CTGATGAGTT GGGCTTATTT GATGTACTCG CGCCCTGGGG TGTACTATAG

27851 CCGGGTCAAC GGAATACGCG CCCACCGAAA CCGAATTCTC CTGGAACAGG
GGCCAGTTG CCTATGCGC GGGTGGCTTT GGCTTAAGAG GACCTTGTC

27901 CGGCTATTAC CACCACACCT CGTAATAACC TTAATCCCCG TAGTTGGCCC
GCCGATAATG GTGGTGTGGA GCATTATTGG AATTAGGGGC ATCAACCGGG

27951 GCTGCCCTGG TGTACCAGGA AAGTCCCGCT CCCACCACTG TGGTACTTCC
CGACGGGACC ACATGGTCCT TTCAGGGCGA GGGTGGTGAC ACCATGAAGG

28001 CAGAGACGCC CAGGCCGAAG TTCAGATGAC TAACTCAGGG GCGCAGCTTG
GTCTCTGCGG GTCCGGCTTC AAGTCTACTG ATTGAGTCCC CGCGTCGAAC

28051 CGGGCGGCTT TCGTCACAGG GTGCGGTCGC CCGGGCAGGG TATAACTCAC
GCCCGCCGAA AGCAGTGTCC CACGCCAGCG GGCCCGTCCC ATATTGAGTG

28101 CTGACAATCA GAGGGCGAGG TATTCAGCTC AACGACGAGT CGGTGAGCTC
GACTGTTAGT CTCCGCTCC ATAAGTCGAG TTGCTGCTCA GCCACTCGAG

28151 CTCGCTTGGT CTCCGTCCGG ACGGGACATT TCAGATCGGC GGCGCCGGCC
GAGCGAACCA GAGGCAGGCC TGCCCTGTAA AGTCTAGCCG CCGCGGCCGG

28201 GCTCTTCATT CACGCCTCGT CAGGCAATCC TAACTCTGCA GACCTCGTCC
CGAGAAGTAA GTGCGGAGCA GTCCGTTAGG ATTGAGACGT CTGGAGCAGG

28251 TCTGAGCCGC GCTCTGGAGG CATTGGAAT CTGCAATTTA TTGAGGAGTT
AGACTCGGCG CGAGACCTCC GTAACCTTGA GACGTAAAT AACTCCTCAA

28301 TGTGCCATCG GTCTACTTTA ACCCCTTCTC GGGACCTCCC GGCCACTATC
ACACGGTAGC CAGATGAAAT TGGGGAAGAG CCCTGGAGGG CCGGTGATAG

28351 CGGATCAATT TATTCCTAAC TTTGACGCGG TAAAGGACTC GGCGGACGGC
GCCTAGTTAA ATAAGGATTG AACTGCGCC ATTTCTGAG CCGCCTGCCG

28401 TACGACTGAA TGTTAAGTGG AGAGGCAGAG CAACTGCGCC TGAAACACCT
ATGCTGACTT ACAATTCACC TCTCCGTCTC GTTGACGCGG ACTTTGTGGA

Figure 26 AD

28451 GGTCCACTGT CGCCGCCACA AGTGCTTTGC CCGCGACTCC GGTGAGTTT
CCAGGTGACA GCGGCGGTGT TCACGAAACG GCGGCTGAGG CCACTCAAAA

28501 GCTACTTTGA ATTGCCCCGAG GATCATATCG AGGGCCCCGGC GCACGGCGTC
CGATGAAACT TAACGGGCTC CTAGTATAGC TCCCGGGCCG CGTGCCCGAG

28551 CGGCTTACCG CCCAGGGAGA GCTTGCCCGT AGCCTGATTC GGGAGTTTAC
GCCGAATGGC GGGTCCCTCT CGAACGGGCA TCGGACTAAG CCCTCAAATG

28601 CCAGCGCCCC CTGCTAGTTG AGCGGGACAG GGGACCCTGT GTTCTCACTG
GGTCGCGGGG GACGATCAAC TCGCCCTGTC CCCTGGGACA CAAGAGTGAC

28651 TGATTTGCAA CTGTCCTAAC CCTGGATTAC ATCAAGATCT TTGTTGCCAT
ACTAAACGTT GACAGGATTG GGACCTAATG TAGTTCTAGA AACAAACGTA

28701 CTCTGTGCTG AGTATAATAA ATACAGAAAT TAAAATATAC TGGGGCTCCT
GAGACACGAC TCATATTATT TATGTCTTTA ATTTTATATG ACCCCGAGGA

28751 ATCGCCATCC TGTAACGCC ACCGTCTTCA CCCGCCCAAG CAAACCAAGG
TAGCGGTAGG ACATTTGCGG TGGCAGAACT GGGCGGGTTC GTTGTGGTTC

28801 CGAACCTTAC CTGGTACTTT TAACATCTCT CCCTCTGTGA TTTACAACAG
GCTTGGAATG GACCATGAAA ATTGTAGAGA GGGAGACACT AAATGTTGTC

28851 TTTCAACCCA GACGGAGTGA GTCTACGAGA GAACCTCTCC GAGCTCAGCT
AAAGTTGGGT CTGCCTCACT CAGATGCTCT CTTGGAGAGG CTCGAGTCGA

28901 ACTCCATCAG AAAAAACACC ACCCTCCTTA CCTGCCGGGA ACGTACGAGT
TGAGGTAGTC TTTTGTGGG TGGGAGGAAT GGACGGCCCT TGCATGCTCA

28951 GCGTCACCGG CCGCTGCACC ACACCTACCG CCTGACCGTA AACCAGACTT
CGCAGTGCCG GCGACGTGG TGTGGATGGC GGAAGTGGAT TTGGTCTGAA

29001 TTTCCGGACA GACCTCAATA ACTCTGTTTA CCAGAACAGG AGGTGAGCTT
AAAGGCCTGT CTGGAGTTAT TGAGACAAAT GGTCTTGTCC TCCACTCGAA

29051 AGAAAACCTT TAGGGTATTA GGCCAAAGGC GCAGCTACTG TGGGGTTTAT
TCTTTTGGGA ATCCCATAAAT CCGGTTTCCG CGTCGATGAC ACCCCAAATA

29101 GAACAATTCA AGCAACTCTA CGGGCTATTG TAATTCAGGT TTCTCTAGAA
CTTGTTAAGT TCGTTGAGAT GCGCGATAAG ATTAAGTCCA AAGAGATCTT

29151 TCGGGGTTGG GGTATTCTC TGTCTTGTA TTCTCTTTAT TCTTATACTA
AGCCCCAACC CCAATAAGAG ACAGAACACT AAGAGAAATA AGAATATGAT

29201 ACGCTTCTCT GCCTAAGGCT CGCCGCCTGC TGTGTGCACA TTTGCATTTA
TGCGAAGAGA CGGATTCCGA GCGGCGGACG ACACACGTGT AAACGTAAAT

29251 TTGTCAGCTT TTTAAACGCT GGGGTCGCCA CCAAGATGA TTAGGTACAT
AACAGTCGAA AAATTTGCGA CCCCAGCGGT GGGTCTACT AATCCATGTA

29301 AATCCTAGGT TTAATCAGCT TTGCGTCAGC CCACGGTACC ACCCAAAAGG
TTAGGATCCA AATGAGTGGG AACGCAGTCG GGTGCCATGG TGGGTTTTC

29351 TGGATTTTAA GGAGCCAGCC TGTAATGTTA CATTGCGAGC TGAAGCTAAT
ACCTAAAATT CCTCGGTCGG ACATTACAAT GTAAGCGTCG ACTTCGATTA

Figure 26 AE

29451 TCGCCACAAA AACAAAATTG GCAAGTATGC TGTATTATGCT ATTTGGCAGC
AGCGGTGTTT TTGTTTAAAC CGTTCATACG ACAAATACGA TAAACCGTCG

29501 CAGGTGACAC TACAGAGTAT AATGTTACAG TTTTCCAGGG TAAAAGTCAT
GTCCACTGTG ATGTCTCATA TTACAATGTC AAAAGGTCCC ATTTTCAGTA

29551 AAAACTTTTA TGTATACTTT TCCATTTTAT GAAATGTGCG ACATTACCAT
TTTGTAAAT ACATATGAAA AGGTAAATA CTTTACACGC TGTAAATGGTA

29601 GTACATGAGC AAACAGTATA AGTTGTGGCC CCCACAAAAT TGTGTGAAA
CATGTACTCG TTTGTCTATAT TCAACACCGG GGGTGTTTTA ACACACCTTT

29651 ACACTGGCAC TTTCTGCTGC ACTGCTATGC TAATTACAGT GCTCGCTTTG
TGTGACCGTG AAAGACGACG TGACGATACG ATTAATGTCA CGAGCGAAAC

29701 GTCTGTACCC TACTCTATAT TAAATACAAA AGCAGACGCA GCTTTATTGA
CAGACATGGG ATGAGATATA ATTTATGTTT TCGTCTGCGT CGAAATAACT

29751 GGAAAAGAAA ATGCCTTAAT TTACTAAGTT ACAAAGCTAA TGTCACCACT
CCTTTTCTTT TACGGAATTA AATGATTCAA TGTTTCGATT ACAGTGGTGA

29801 AACTGCTTTA CTCGCTGCTT GCAAAACAAA TTCAAAAAGT TAGCATTATA
TTGACGAAAT GAGCGACGAA CGTTTTGTTT AAGTTTTTCA ATCGTAATAT

29851 ATTAGAATAG GATTTAAACC CCCCAGTCAT TTCCTGCTCA ATACCATTCC
TAATCTTATC CTAAATTTGG GGGGCCAGTA AAGGACGAGT TATGGTAAGG

29901 CCTGAACAAT TGACTCTATG TGGGATATGC TCCAGCGCTA CAACCTTGAA
GGACTTGTTA ACTGAGATAC ACCCTATACG AGGTCGCGAT GTTGGAACCT

29951 GTCAGGCTTC CTGGATGTCA GCATCTGACT TTGGCCAGCA CCTGTCCCGC
CAGTCCGAAG GACCTACAGT CGTAGACTGA AACCAGGTCGT GGACAGGGCG

30001 GGATTTGTTC CAGTCCAAC ACAGCGACCC ACCCTAACAG AGATGACCAA
CCTAAACAAG GTCAGGTTGA TGTGCTGGG TGGGATTGTC TCTACTGGTT

30051 CACAACCAAC GCGGCCGCCG CTACCGGACT TACATCTACC ACAAATACAC
GTGTTGGTTG CGCCGGCGGC GATGGCCTGA ATGTAGATGG TGTTTATGTG

30101 CCCAAGTTTC TGCCTTTGTC AATAACTGGG ATAACCTGGG CATGTGGTGG
GGTTCAAAG ACGGAACAG TTATTGACCC TATTGAACCC GTACACCACC

30151 TTCTCCATAG CGCTTATGTT TGTATGCCTT ATTATTATGT GGCTCATCTG
AAGAGGTATC GCGAATACAA ACATACGAA TAATAATACA CCGAGTAGAC

30201 CTGCCTAAAG CGCAAACGCG CCCGACCACC CATCTATAGT CCCATCATTG
GACGGATTTC GCGTTTGCGC GGGCTGGTGG GTAGATATCA GGGTAGTAAC

30251 TGCTACACCC AAACAATGAT GGAATCCATA GATTGGACGG ACTGAAACAC
ACGATGTGGG TTTGTTACTA CCTTAGGTAT CTAACCTGCC TGACTTTGTG

30301 ATGTTCTTTT CTCTTACAGT ATGATTAAAT GAGACATGAT TCCTCGAGTT
TACAAGAAA GAGAATGTCA TACTAATTTA CTCTGTACTA AGGAGCTCAA

Figure 26 AF

30401 TGC GGTTTCT CACATCGAAG TAGACTGCAT TCCAGCCTTC ACAGTCTATT
 ACGCCAAAGA GTGTAGCTTC ATCTGACGTA AGGTCGGAAG TGTCAGATAA
 30451 TGCTTTACGG ATTTGTCACC CTCACGCTCA TCTGCAGCCT CATCACTGTG
 ACGAAATGCC TAAACAGTGG GAGTCCGAGT AGACGTCGGA GTAGTGACAC
 30501 GTCATCGCCT TTATCCAGTG CATTGACTGG GTCTGTGTGC GCTTTGCATA
 CAGTAGCGGA AATAGGTCAC GTAAGTACC CAGACACACG CGAAACGTAT
 30551 TCTCAGACAC CATCCCCAGT ACAGGGACAG GACTATAGCT GAGCTTCTTA
 AGAGTCTGTG GTAGGGGTCA TGTCCCTGTC CTGATATCGA CTCGAAGAAT
 30601 GAATTCCTTA ATTATGAAAT TTACTGTGAC TTTTCTGCTG ATTATTGCA
 CTTAAGAAAT TAATACTTTA AATGACACTG AAAAGACGAC TAATAAACGT
 30651 CCCTATCTGC GTTTTGTTC CCGACCTCCA AGCCTCAAAG ACATATATCA
 GGGATAGACG CAAAACAAGG GGCTGGAGGT TCGGAGTTTC TGTATATAGT
 30701 TGCAGATTCA CTCGTATATG GAATATTCCA AGTTGCTACA ATGAAAAAAG
 ACGTCTAAGT GAGCATATAC CTTATAAGGT TCAACGATGT TACTTTTTTC
 30751 CGATCTTTCC GAAGCCTGGT TATATGCAAT CATCTCTGTT ATGGTGTCTT
 GCTAGAAAGG CTTCCGACCA ATATACGTTA GTAGAGACAA TACCACAAGA
 30801 GCAGTACCAT CTTAGCCCTA GCTATATATC CCTACCTTGA CATTGGCTGG
 CGTCATGGTA GAATCGGGAT CGATATATAG GGATGGAACGT GTAACCGACC
 30851 AACGCAATAG ATGCCATGAA CCACCCAACCT TTCCCCGCGC CCGCTATGCT
 TTGCGTTATC TACGGTACTT GGTGGGTGTA AAGGGGCGCG GCGGATACGA
 30901 TCCACTGCAA CAAGTTGTTG CCGGCGGCTT TGTCCCAGCC AATCAGCCTC
 AGGTGACGTT GTTCAACAAC GGCCGCCGAA ACAGGGTCGG TTAGTCGGAG
 30951 GCCCACCTTC TCCCACCCCC ACTGAAATCA GCTACTTTAA TCTAACAGGA
 CGGGTGGAAG AGGGTGGGGG TGACTTTAGT CGATGAAATT AGATTGTCCT
 31001 GGAGATGACT GACACCCTAG ATCTAGAAAT GGACGGAATT ATTACAGAGC
 CCTCTACTGA CTGTGGGATC TAGATCTTTA CCTGCCTTAA TAATGTCTCG
 31051 AGCGCCTGCT AGAAAGACGC AGGGCAGCGG CCGAGCAACA GCGCATGAAT
 TCGCGGACGA TCTTTCTGCG TCCCGTCGCC GGCTCGTTGT CCGCTACTTA
 31101 CAAGAGCTCC AAGACATGGT TAACTTGAC CAGTGCAAAA GGGGTATCTT
 GTTCTCGAGG TTCTGTACCA ATTGAACGTG GTCACGTTTT CCCCATAGAA
 31151 TTGTCTCGTA AAGCAGGCCA AAGTCACCTA CGACAGTAAT ACCACCGGAC
 AACAGAGCAT TTCGTCCGGT TTCAGTGGAT GCTGTCATTA TGGTGGCCTG
 31201 ACCGCCTTAG CTACAAGTTG CCAACCAAGC GTCAGAAATT GGTGGTCATG
 TGGCGGAATC GATGTTCAAC GGTGGGTTTC CAGTCTTTAA CCACCAGTAC
 31251 GTGGGAGAAA AGCCCATTA CATAACTCAG CACTCGGTAG AAACCGAAGG
 CACCCCTCTT TCGGGTAATG GTATTGAGTC GTGAGCCATC TTTGGCTTCC

Figure 26 AG

31351 AGACCCTGTG CGGTCTCAAA GATCTTATTC CCTTTAACTA ATAAAAAAAA
 TCTGGGACAC GCCAGAGTTT CTAGAATAAG GGAAATTGAT TATTTTTTTT
 31401 ATAATAAAGC ATCACTTACT TAAAATCAGT TAGCAAATTT CTGTCCAGTT
 TATTATTTTC TAGTGAATGA ATTTTAGTCA ATCGTTTAAA GACAGGTCAA
 31451 TATTTCAGCAG CACCTCCTTG CCCTCCTCCC AGCTCTGGTA TTGCAGCTTC
 ATAAGTCGTC GTGGAGGAAC GGGAGGAGGG TCGAGACCAT AACGTCGAAG
 31501 CTCCTGGCTG CAAACTTTCT CCACAATCTA AATGGAATGT CAGTTTCCTC
 GAGGACCGAC GTTTGAAAGA GGTGTAGAT TTACCTTACA GTCAAAGGAG
 31551 CTGTTCTGT CCATCCGCAC CCACTATCTT CATGTTGTTG CAGATGAAGC
 GACAAGGACA GGTAGGCGTG GGTGATAGAA GTACAACAAC GTCTACTTCG
 31601 GCGCAAGACC GTCTGAAGAT ACCTTCAACC CCGTGTATCC ATATGACACG
 CGCGTTCTGG CAGACTTCTA TGGAGTTGG GGCACATAGG TATACTGTGC
 31651 GAAACCGGTC CTCCAACGTG GCCTTTTCTT ACTCCTCCCT TTGTATCCCC
 CTTTGCCAG GAGGTTGACA CGGAAAAGAA TGAGGAGGGA AACATAGGGG
 31701 CAATGGGTTT CAAGAGAGTC CCCCTGGGGT ACTCTCTTTG CGCCTATCCG
 GTTACCCAAA GTTCTCTCAG GGGGACCCCA TGAGAGAAAC GCGGATAGGC
 31751 AACCTCTAGT TACCTCCAAT GGCATGCTTG CGCTCAAAAT GGGCAACGGC
 TTGGAGATCA ATGGAGGTTA CCGTACGAAC GCGAGTTTAA CCCGTTGCCG
 31801 CTCTCTCTGG ACGAGGCCGG CAACCTTACC TCCCAAAATG TAACCACTGT
 GAGAGAGACC TGCTCCGGCC GTTGGAATGG AGGGTTTAC ATTGGTGACA
 31851 GAGCCACCT CTCAAAAAA CCAAGTCAAA CATAAACCTG GAAATATCTG
 CTCGGGTGGA GAGTTTTTTT GGTTCAGTTT GTATTGGAC CTTTATAGAC
 31901 CACCCCTCAC AGTTACCTCA GAAGCCCTAA CTGTGGCTGC CGCCGCACCT
 GTGGGGAGTG TCAATGGAGT CTTCCGGATT GACACCGACG GCGGCGTGGA
 31951 CTAATGGTCG CGGGCAACAC ACTCACCATG CAATCACAGG CCCCCTAAC
 GATTACCAGC GCGGTTGTG TGAGTGGTAC GTTAGTGTCC GGGGCGATTG
 32001 CGTGCACGAC TCCAAACTTA GCATTGCCAC CCAAGGACCC CTCACAGTGT
 GCACGTGCTG AGGTTTGAAT CGTAACGGTG GGTTCCTGGG GAGTGTCA
 32051 CAGAAGGAAA GCTAGCCCTG CAAACATCAG GCCCCCTCAC CACCACCGAT
 GTCTTCCTTT CGATCGGGAC GTTTGTAGTC CGGGGGAGTG GTGGTGCTA
 32101 AGCAGTACCC TTACTATCAC TGCCTCACC CCTCTAACTA CTGCCACTGG
 TCGTCATGGG AATGATAGTG ACGGAGTGGG GGAGATTGAT GACGGTGACC
 32151 TAGCTTGCGC ATTGACTTGA AAGAGCCCAT TTATACACAA AATGGAAAC
 ATCGAACCCG TAACTGAAC TCTCGGGTA AATATGTGTT TTACCTTTTG
 32201 TAGGACTAAA GTACGGGGCT CCTTTGCATG TAACAGACGA CCTAAACACT
 ATCCTGATTT CATGCCCGA GGAAACGTAC ATTGTCTGCT GGATTGTGA

Figure 26 AH

32301 AACTAAAGTT ACTGGAGCCT TGGGTTTTGA TTCACAAGGC AATATGCAAC
 TTGATTTCAA TGACCTCGGA ACCCAAACT AAGTGTTCG TTATACGTTG
 32351 TTAATGTAGC AGGAGGACTA AGGATTGATT CTCAAAACAG ACGCCTTATA
 AATTACATCG TCCTCCTGAT TCCTAACTAA GAGTTTGTG TGCGGAATAT
 32401 CTTGATGTTA GTTATCCGTT TGATGCTCAA AACCAACTAA ATCTAAGACT
 GAACTACAAT CAATAGGCAA ACTACGAGT TTGGTTGATT TAGATTCTGA
 32451 AGGACAGGGC CCTCTTTTTA TAAACTCAGC CCACAACCTG GATATTAACT
 TCCTGTCCCG GGAGAAAAAT ATTTGAGTCG GGTGTGAAC CTATAATTGA
 32501 ACAACAAAGG CCTTTACTTG TTTACAGCTT CAAACAATTC CAAAAAGCTT
 TGTGTGTTCC GGAAATGAAC AAATGTCGAA GTTTGTTAAG GTTTTTCGAA
 32551 GAGGTAAACC TAAGCACTGC CAAGGGGTTG ATGTTTGACG CTACAGCCAT
 CTCCAATTGG ATTCGTGACG GTTCCCAAC TACAACTGC GATGTCGGTA
 32601 AGCCATTAAT GCAGGAGATG GGCTTGAATT TGGTTCACCT AATGCACCAA
 TCGGTAATTA CGTCCTCTAC CCGAACTTAA ACCAAGTGGA TTACGTGGTT
 32651 ACACAAATCC CCTCAAAACA AAAATTGGCC ATGGCCTAGA ATTTGATTCA
 TGTGTTTAGG GGAGTTTTGT TTTTAACCGG TACCGGATCT TAAACTAAGT
 32701 AACAAGGCTA TGGTTCCTAA ACTAGGAACT GGCCTTAGTT TTGACAGCAC
 TTGTTCCGAT ACCAAGGATT TGATCCTTGA CCGGAATCAA AACTGTCGTG
 32751 AGGTGCCATT ACAGTAGGAA AAAAAATAA TGATAAGCTA ACTTTGTGGA
 TCCACGGTAA TGTCATCCTT TGTTTTTATT ACTATTCGAT TGAAACACCT
 32801 CCACACCAGC TCCATCTCCT AACTGTAGAC TAAATGCAGA GAAAGATGCT
 GGTGTGGTCG AGGTAGAGGA TTGACATCTG ATTTACGTCT CTTTCTACGA
 32851 AAACTCACTT TGGTCTTAAC AAAATGTGGC AGTCAAATAC TTGCTACAGT
 TTTGAGTGAA ACCAGAATTG TTTTACACCG TCAGTTTATG AACGATGTCA
 32901 TTCAGTTTTG GCTGTAAAG GCAGTTTGGC TCCAATATCT GGAACAGTTC
 AAGTCAAAAC CGACAATTTC CGTCAAACCG AGGTTATAGA CTTGTCAAG
 32951 AAAGTGCTCA TCTTATTATA AGATTTGACG AAAATGGAGT GCTACTAAAC
 TTTCACGAGT AGAATAATAT TCTAACTGC TTTTACCTCA CGATGATTTG
 33001 AATTCCTTCC TGGACCCAGA ATATTGGAAC TTTAGAAATG GAGATCTTAC
 TTAAGGAAGG ACCTGGGTCT TATAACCTTG AAATCTTTAC CTCTAGAATG
 33051 TGAAGGCACA GCCTATACAA ACGCTGTTGG ATTTATGCCT AACCTATCAG
 ACTTCCGTGT CGGATATGTT TGCGACAACC TAAATACGGA TTGGATAGTC
 33101 CTTATCCAAA ATCTCACGGT AAAACTGCCA AAAGTAACAT TGTCAGTCAA
 GAATAGGTTT TAGAGTGCCA TTTTGACGGT TTTCATTGTA ACAGTCAGTT
 33151 GTTTACTTAA ACGGAGACAA AACTAAACCT GTAACACTAA CCATTACACT
 CAAATGAATT TGCCTCTGTT TTGATTGGA CATTGTGATT GGTAATGTGA

Figure 26 AI

33251 CATTTCATG GGA CTGGTCT GGCCACA ACT ACATTAATGA AATATTTGCC
GTAAAAGTAC CCTGACCAGA CCGGTGTTGA TGTAATTACT TTATAAACGG

33301 ACATCCTCTT AACTTTTTT ATACATTGCC CAAGAATAAA GAATCGTTTG
TG TAGGAGAA TGTGAAAAAG TATGTAACGG GTTCTTATTT CTTAGCAAA C

33351 TGT TATGTTT CAACGTGTTT ATTTTTC AAT TGCAGAAAAT TTCAAGTCAT
ACAATACAAA GTTGACAAA TAAAAAGTTA ACGTCTTTTA AAGTTCAGTA

33401 TTTTCATTCA GTAGTATAGC CCCACCACCA CATAGCTTAT ACAGATCACC
AAAAGTAAGT CATCATATCG GGGTGGTGGT GTATCGAATA TGTCTAGTGG

33451 GTACCTTAAT CAAACTCACA GAACCCTAGT ATTCAACCTG CCACCTCCCT
CATGGAATTA GTTTGAGTGT CTTGGGATCA TAAGTTGGAC GGTGGAGGGA

33501 CCCAACACAC AGAGTACACA GTCCTTTCTC CCCGGCTGGC CTTAAAAAGC
GGGTTGTGTG TCTCATGTGT CAGGAAAGAG GGGCCGACCG GAATTTTTCG

33551 ATCATATCAT GGGTAACAGA CATATTCTTA GGTGTTATAT TCCACACGGT
TAGTATAGTA CCCATTGTCT GTATAAGAAT CCACAATATA AGGTGTGCCA

33601 TTCCTGTGCA GCCAAACGCT CATCAGTGAT ATTAATAAAC TCCCCGGGCA
AAGGACAGCT CGGTTTGCGA GTAGTCACTA TAATTATTG AGGGGCCCGT

33651 GCTCACTTAA GTTCATGTCG CTGTCCAGCT GCTGAGCCAC AGGCTGCTGT
CGAGTGAATT CAAGTACAGC GACAGGTGCA CGACTCGGTG TCCGACGACA

33701 CCAACTTGCG GTTGCTTAAC GGGCGGCGAA GGAGAAGTCC ACGCCTACAT
GGTTGAACGC CAACGAATTG CCCGCCGCTT CCTCTTCAGG TGCGGATGTA

33751 GGGGGTAGAG TCATAATCGT GCATCAGGAT AGGGCGGTGG TGCTGCAGCA
CCCCATCTC AGTATTAGCA CGTAGTCCTA TCCCGCCACC ACGACGTCGT

33801 GCGCGCGAAT AACTGCTGC CGCCGCCGCT CCGTCCTGCA GGAATACAAC
CGCGCGCTTA TTTGACGACG GCGGCGGCGA GGCAGGACGT CTTTATGTTG

33851 ATGGCAGTGG TCTCCTCAGC GATGATTCGC ACCGCCCGCA GCATAAGGCG
TACCGTCACC AGAGGAGTCG CTAATAAGCG TGGCGGGCGT CGTATTCCGC

33901 CCTTGTCCTC CGGGCACAGC AGCGCACCCCT GATCTCACTT AAATCAGCAC
GGAACAGGAG GCCCGTGTCG TCGCGTGGGA CTAGAGTGAA TTTAGTCGTG

33951 AGTAACTGCA GCACAGCACC ACAATATTGT TCAAAATCCC ACAGTGCAAG
TCATTGACGT CGTGTCGTGG TGTATAACA AGTTTTAGGG TGTCACGTT C

34001 GCGCTGTATC CAAAGCTCAT GCGGGGGACC ACAGAACCCA CGTGCCCATC
CGCGACATAG GTTTCGAGTA CCGCCCCCTGG TGTCTTGGGT GCACCGGTAG

34051 ATACCACAAG CGCAGGTAGA TTAAGTGGCG ACCCCTCATA AACACGCTGG
TATGGTGTT CCGTCCATCT AATTCACCGC TGGGGAGTAT TTGTGCGACC

34101 ACATAACAT TACCTCTTTT GGCATGTTGT AATTCACCAC CTCCCGGTAC
TGTATTTGTA ATGGAGAAAA CCGTACAACA TTAAGTGGTG GAGGGCCATG

Figure 26 AJ

34201 GCTGGCCAAA ACCTGCCCCG CGGCTATACA CTGCAGGGAA CCGGGACTGG
CGACCGGTTT TGGACGGGCG GCCGATATGT GACGTCCCTT GGCCCTGACC

34251 AACAATGACA GTGGAGAGCC CAGGACTCGT AACCATGGAT CATCATGCTC
TTGTTACTGT CACCTCTCGG GTCCTGAGCA TTGGTACCTA GTAGTACGAG

34301 GTCATGATAT CAATGTTGGC ACAACACAGG CACACGTGCA TACACTTCCT
CAGTACTATA GTTACAACCG TGTGTGTGCC GTGTGCACGT ATGTGAAGGA

34351 CAGGATTACA AGCTCCTCCC GCGTTAGAAC CATATCCCAG GGAACAACCC
GTCCTAATGT TCGAGGAGGG CGCAATCTTG GTATAGGGTC CCTTGTGGG

34401 ATTCTGAAT CAGCGTAAAT CCCACACTGC AGGGAAGACC TCGCACGTAA
TAAGGACTTA GTCGCATTTA GGGTGTGACG TCCCTTCTGG AGCGTGCATT

34451 CTCACGTTGT GCATTGTCAA AGTGTTACAT TCGGGCAGCA GCGGATGATC
GAGTGCAACA CGTAACAGTT TCACAATGTA AGCCCGTCGT CGCCTACTAG

34501 CTCCAGTATG GTAGCGCGGG TTTCTGTCTC AAAAGGAGGT AGACGATCCC
GAGGTCATAC CATCGCGCCC AAAGACAGAG TTTTCTCCA TCTGCTAGGG

34551 TACTGTACGG AGTGCGCCGA GACAACCGAG ATCGTGTTGG TCGTAGTGTC
ATGACATGCC TCACGCGGCT CTGTTGGCTC TAGCACAACC AGCATCACAG

34601 ATGCCAAATG GAACGCCGGA CGTAGTCATA TTTCTGAAG CAAAACCAGG
TACGGTTTAC CTTGCGGCCT GCATCAGTAT AAAGGACTTC GTTTTGGTCC

34651 TGCGGGCGTG ACAAACAGAT CTGCGTCTCC GGTCTCGCCG CTTAGATCGC
ACGCCCACAC TGTGTGTCTA GACGCAGAGG CCAGAGCGGC GAATCTAGCG

34701 TCTGTGTAGT AGTTGTAGTA TATCCACTCT CTCAAAGCAT CCAGGCGCCC
AGACACATCA TCAACATCAT ATAGGTGAGA GAGTTTCGTA GGTCCGCGGG

34751 CCTGGCTTCG GGTTCATGT AAACCTCCTC ATGCGCCGCT GCCCTGATAA
GGACCGAAGC CCAAGATACA TTTGAGGAAG TACGCGGCGA CGGGACTATT

34801 CATCCACCAC CGCAGAATAA GCCACACCCA GCCAACCTAC ACATTGCTTC
GTAGGTGGTG GCGTCTTATT CGGTGTGGGT CGGTTGGATG TGTAAAGCAAG

34851 TGCGAGTCAC ACACGGGAGG AGCGGGAAGA GCTGGAAGAA CCATGTTTTT
ACGCTCAGTG TGTGCCCTCC TCGCCCTTCT CGACCTTCTT GGTACAAAAA

34901 TTTTTTATTC CAAAAGATTA TCCAAAACCT CAAAATGAAG ATCTATTAAG
AAAAAATAAG GTTTTCTAAT AGGTTTTGGA GTTTTACTTC TAGATAATTC

34951 TGAACGCGCT CCCCTCCGGT GCGGTGGTCA AACTCTACAG CCAAAGAACA
ACTTGCGCGA GGGGAGGCCA CCGCACCAGT TTGAGATGTC GGTTCCTTGT

35001 GATAATGGCA TTTGTAAGAT GTTGCACAAT GGCTTCCAAA AGGCAAAACGG
CTATTACCGT AAACATTCTA CAACGTGTTA CCGAAGGTTT TCCGTTTGCC

35051 CCCTCACGTC CAAGTGGACG TAAAGGCTAA ACCCTTCAGG GTGAATCTCC
GGGAGTGCAG GTTCACCTGC ATTTCCGATT TGGGAAGTCC CACTTAGAGG

Figure 26 AK

35151 CCACCTTCTC AATATATCTC TAAGCAAATC CCGAATATTA AGTCCGGCCA
GGTGGAGAG TTATATAGAG ATTCTGTTTAG GGCTTATAAT TCAGGCCGGT

35201 TTGTAAAAAT CTGCTCCAGA GCGCCCTCCA CCTTCAGCCT CAAGCAGCGA
AACATTTTAA GACGAGGTCT CGCGGGAGGT GGAAGTCGGA GTTCGTCGCT

35251 ATCATGATTG CAAAAATTCA GGTTCCTCAC AGACCTGTAT AAGATTCAAA
TAGTACTAAC GTTTTAAAGT CCAAGGAGTG TCTGGACATA TTCTAAGTTT

35301 AGCGGAACAT TAACAAAAAT ACCGCGATCC CGTAGGTCCC TTCGCAGGGC
TCGCCCTGTA ATGTGTTTTA TGGCGCTAGG GCATCCAGGG AAGCGTCCC

35351 CAGCTGAACA TAATCGTGCA GGTCTGCACG GACCAGCGCG GCCACTTCCC
GTCGACTTGT ATTAGCACGT CCAGACGTGC CTGGTCGCGC CGGTGAAGGG

35401 CGCCAGGAAC CATGACAAAA GAACCCACAC TGATTATGAC ACGCATACTC
GCGGTCTTG GTACTGTTTT CTGGGTGTG ACTAATACTG TGCGTATGAG

35451 GGAGCTATGC TAACCAGCGT AGCCCCGATG TAAGCTTGTT GCATGGGCGG
CCTCGATACG ATTGGTCGCA TCGGGGCTAC ATTCGAACAA CGTACCCGCC

35501 CGATATAAAA TGCAAGGTGC TGCTCAAAAA ATCAGGCAAA GCCTCGCGCA
GCTATATTTT ACGTTCACG ACGAGTTTTT TAGTCCGTTT CGGAGCGCGT

35551 AAAAAAGAAAG CACATCGTAG TCATGCTCAT GCAGATAAAG GCAGGTAAGC
TTTTCTTTC GTGTAGCATC AGTACGAGTA CGTCTATTTC CGTCCATTGC

35601 TCCGGAACCA CCACAGAAAA AGACACCATT TTTCTCTCAA ACATGTCTGC
AGGCCTTGGT GGTGTCTTTT TCTGTGGTAA AAAGAGAGTT TGTACAGACG

35651 GGGTTTCTGC ATAAACACAA AATAAAATAA CAAAAAACA TTAAACATT
CCCAAAGACG TATTTGTGTT TTATTTTATT GTTTTTTGT AAATTTGTAA

35701 AGAAGCCTGT CTTACAACAG GAAAAACAAC CCTTATAAGC ATAAGACGGA
TCTTCGGACA GAATGTTGTC CTTTTGTG GGAATATTGC TATTCTGCCT

35751 CTACGGCCAT GCCGGCGTGA CCGTAAAAAA ACTGGTCACC GTGATTAAAA
GATGCCGGTA CGGCCGCACT GGCATTTTTT TGACCAGTGG CACTAATTTT

35801 AGCACCACCG ACAGCTCCTC GGTATGTCC GGAGTCATAA TGTAAGACTC
TCGTGGTGGC TGTCGAGGAG CCAGTACAGG CCTCAGTATT ACATTCTGAG

35851 GGTAAACACA TCAGGTTGAT TCACATCGGT CAGTGCTAAA AAGCGACCGA
CCATTTGTGT AGTCCAATA AGTGTAGCCA GTCACGATTT TTCGCTGGCT

35901 AATAGCCCGG GGAATACAT ACCCGCAGGC GTAGAGACAA CATTACAGCC
TTATCGGGCC CCCTTATGTA TGGGCGTCCG CATCTCTGTT GTAATGTCGG

35951 CCCATAGGAG GTATAACAAA ATTAATAGGA GAGAAAAACA CATAAACACC
GGGTATCCTC CATATTGTTT TAATTATCCT CTCTTTTGT GTATTTGTGG

36001 TGAAAAACCC TCCTGCCTAG GCAAAATAGC ACCCTCCCGC TCCAGAACAA
ACTTTTGGG AGGACGGATC CGTTTTATCG TGGGAGGGCG AGGTCTTGTT

Figure 26 AL

36101 AAAGAAAACC TATTAATAAA ACACCACTCG ACACGGCACC AGCTCAATCA
 TTTCTTTTGG ATAATTTTTT TGTGGTGAGC TGCGCCGTGG TCGAGTTAGT
 36151 GTCACAGTGT AAAAAAGGGC CAAGTGCAGA GCGAGTATAT ATAGGACTAA
 CAGTGTCACT TTTTTCCTCG GTTCACGTCT CGCTCATATA TATCCTGATT
 36201 AAAATGACGT AACGGTTAAA GTCCACAAAA AACACCCAGA AAACCGCACG
 TTTTACTGCA TTGCCAATTT CAGGTGTTTT TTGTGGGTCT TTTGGCGTGC
 36251 CGAACCTACG CCCAGAAACG AAAGCCAAAA AACCACAAAC TTCCTCAAAT
 GCTTGGATGC GGGTCTTTGC TTTCGGTTTT TTGGGTGTG AAGGAGTTTA
 36301 CGTCACTTCC GTTTTCCAC GTTACGTCAC TTCCCATTTT AAGAAAACTA
 GCAGTGAAGG CAAAAGGGTG CAATGCAGTG AAGGGTAAAA TTCTTTTGAT
 36351 CAATTCCCAA CACATACAAG TTAATCCGCC CTAAACCTA CGTCACCCGC
 GTTAAGGGTT GTGTATGTTT AATGAGGCGG GATTTTGGAT GCAGTGGGCG
 36401 CCCGTTCCTA CGCCCGCGC CACGTCACAA ACTCCACCCC CTCATTATCA
 GGGCAAGGGT GCGGGGCGCG GTGCAGTGTT TGAGGTGGGG GAGTAATAGT
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 36451 TATTGGCTTC AATCCAAAAA AAGGTATATT ATTGATGATG TTAATTAAGA
 ATAACCGAAG TTAGGTTTTA TTCCATATAA TAACACTAC AATTAATTCT
 36501 ATTCCGATCT GCGACGCGAG GCTGGATGGC CTTCCCCATT ATGATTCTTC
 TAAGCCTAGA CGCTGCGCTC CGACCTACCG GAAGGGGTAA TACTAAGAAG
 36551 TCGCTTCCGG CGGCATCGGG ATGCCCCGCT TGCAGGCCAT GCTGTCCAGG
 AGCGAAGGCC GCCGTAGCCC TACGGGCGCA ACGTCCGTA CGACAGGTCC
 36601 CAGGTAGATG ACGACCATCA GGGACAGCTT CAAGGCCAGC AAAAGGCCAG
 GTCCATCTAC TGCTGGTAGT CCCTGTCGAA GTTCCGGTCG TTTTCCGGTC
 36651 GAACCGTAAA AAGGCCGCGT TGCTGGCGTT TTTCCATAGG CTCCGCCCCC
 CTTGGCATTT TTCCGGCGCA ACGACCGCAA AAAGGTATCC GAGGCGGGGG
 36701 CTGACGAGCA TCACAAAAAT CGACGCTCAA GTCAGAGGTG GCGAAACCCG
 GACTGCTCGT AGTGTTTTTA GCTGCGAGTT CAGTCTCCAC CGCTTTGGGG
 36751 ACAGGACTAT AAAGATACCA GCGGTTTCCC CCTGGAAGCT CCCTCGTGCG
 TGTCTGATA TTTCTATGGT CCGCAAAGGG GGACCTTCGA GGGAGCACGC
 36801 CTCTCCTGTT CCGACCTGC CGCTTACCGG ATACCTGTCC GCCTTTCTCC
 GAGAGGACAA GGCTGGGACG GCGAATGGCC TATGGACAGG CGGAAAGAGG
 36851 CTTCCGGGAAG CGTGGCGCTT TCTCATAGCT CACGCTGTAG GTATCTCAGT
 GAAGCCCTTC GCACCGCGAA AGAGTATCGA GTGCGACATC CATAGAGTCA
 36901 TCGGTGTAGG TCGTTCGCTC CAAGCTGGGC TGTGTGCACG AACCCCCCGT
 AGCCACATCC AGCAAGCGAG GTTCGACCCG ACACACGTGC TTGGGGGGCA

Figure 26 AM

37001 CCGTAAGACA CGACTTATCG CCACTGGCAG CAGCCACTGG TAACAGGATT
GCCATTCTGT GCTGAATAGC GGTGACCGTC GTCGGTGACC ATTGTCCTAA

37051 AGCAGAGCGA GGTATGTAGG CGGTGCTACA GAGTTCTTGA AGTGGTGCC
TCGTCTCGCT CCATACATCC GCCACGATGT CTCAAGAACT TCACCACCGG

37101 TAACTACGGC TACTACTAGAA GGACAGTATT TGGTATCTGC GCTCTGCTGA
ATTGATGCCG ATGTGATCTT CCTGTCATAA ACCATAGACG CGAGACGACT

37151 AGCCAGTTAC CTTCGGAAAA AGAGTTGGTA GCTCTTGATC CGGCAAACAA
TCGGTCAATG GAAGCCTTTT TCTCAACCAT CGAGAACTAG GCCGTTTGTT

37201 ACCACCGCTG GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC AGATTACGCG
TGGTGGCGAC CATCGCCACC AAAAAACAA ACGTTCTGTCG TCTAATGCGC

37251 CAGAAAAAAA GGATCTCAAG AAGATCCTTT GATCTTTTCT ACGGGGTCTG
GTCTTTTTTT CCTAGAGTTC TTCTAGGAAA CTAGAAAAGA TGCCCCAGAC

37301 ACGCTCAGTG GAACGAAAAC TCACGTTAAG GGATTTTGGT CATGAGATTA
TGCGAGTCAC CTTGCTTTTG AGTGCAATTC CCTAAAACCA GTACTCTAAT

37351 TCAAAAAGGA TCTTCACCTA GATCCTTTTA AATCAATCTA AAGTATATAT
AGTTTTTCTT AGAAGTGGAT CTAGGAAAAT TTAGTTAGAT TTCATATATA

37401 GAGTAACTT GGTCTGACAG TTACCAATGC TTAATCAGTG AGGCACCTAT
CTCATTTGAA CCAGACTGTC AATGGTTACG AATTAGTCAC TCCGTGGATA

37451 CTCAGCGATC TGTCTATTTT GTTCATCCAT AGTTGCCTGA CTCCCCGTCG
GAGTCGCTAG ACAGATAAAG CAAGTAGGTA TCAACGGACT GAGGGGCAGC

37501 TG TAGATAAC TACGATACGG GAGGGCTTAC CATCTGGCCC CAGTGCTGCA
ACATCTATTG ATGCTATGCC CTCCCGAATG GTAGACCGGG GTCACGACGT

37551 ATGATACCGC GAGACCCACG CTCACCGGCT CCAGATTTAT CAGCAATAAA
TACTATGGCG CTCTGGGTGC GAGTGGCCGA GGTCTAAATA GTCGTTATTT

37601 CCAGCCAGCC GGAAGGGCCG AGCGCAGAAG TGGTCCTGCA ACTTTATCCG
GGTCGGTCGG CCTTCCCGGC TCGCGTCTTC ACCAGGACGT TGAATAGGC

37651 CCTCCATCCA GTCTATTAAT TGTGCGGGG AAGCTAGAGT AAGTAGTTCTG
GGAGGTAGGT CAGATAATTA ACAACGGCCC TTCGATCTCA TTCATCAAGC

37701 CCAGTTAATA GTTTGCGCAA CGTTGTTGCC ATTGCTACAG GCATCGTGGT
GGTCAATTAT CAAACGCGTT GCAACAACGG TAACGATGTC CGTAGCACCA

37751 GTCACGCTCG TCGTTTGGA TGGCTTCATT CAGCTCCGGT TCCCAACGAT
CAGTGCGAGC AGCAAACCAT ACCGAAGTAA GTCGAGGCCA AGGGTTGCTA

37801 CAAGGCGAGT TACATGATCC CCCATGTTGT GCAAAAAAGC GGTTAGCTCC
GTTCCGCTCA ATGTACTAGG GGTACAACA CGTTTTTTCG CCAATCGAGG

37851 TTCGGTCCTC CGATCGTTGT CAGAAGTAAG TTGGCCGCGC TGTTATCACT
AAGCCAGGAG GCTAGCAACA GTCTTCATTC AACCGGCGTC ACAATAGTGA

Figure 26 AN

37951 GATGCTTTTC TGTGACTGGT GAGTACTCAA CCAAGTCATT CTGAGAATAG
CTACGAAAAG AACTGACCA CTCATGAGTT GGTTCAGTAA GACTCTTATC

38001 TGTATGCGGC GACCGAGTTG CTCTTGCCCG GCGTCAACAC GGGATAATAC
ACATACGCCG CTGGCTCAAC GAGAACGGGC CGCAGTTGTG CCCTATTATG

38051 CGCGCCACAT AGCAGAACTT TAAAAGTGCT CATCATTGGA AAACGTTCTT
GCGCGGTGTA TCGTCTTGAA ATTTTCACGA GTAGTAACCT TTTGCAAGAA

38101 CGGGGCGAAA ACTCTCAAGG ATCTTACCGC TGTGAGATC CAGTTCGATG
GCCCCGCTTT TGAGAGTTCC TAGAATGGCG ACAACTCTAG GTCAAGCTAC

38151 TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG
ATTGGGTGAG CACGTGGGTT GACTAGAAGT CGTAGAAAAT GAAAGTGGTC

38201 CGTTTCTGGG TGAGCAAAAA CAGGAAGGCA AAATGCCGCA AAAAAGGGAA
GCAAAGACCC ACTCGTTTTT GTCCTTCCGT TTTACGGCGT TTTTCCCTT

38251 TAAGGGCGAC ACGGAAATGT TGAATACTCA TACTCTTCCT TTTTCAATAT
ATTCCCGCTG TGCCTTTACA ACTTATGAGT ATGAGAAGGA AAAAGTTATA

38301 TATTGAAGCA TTTATCAGGG TTATTGTCTC ATGAGCGGAT ACATATTTGA
ATAACTTCGT AAATAGTCCC AATAACAGAG TACTCGCCTA TGTATAAACT

38351 ATGTATTTAG AAAAATAAAC AAATAGGGGT TCCGCGCACA TTTCCCGAA
TACATAAATC TTTTATTTG TTTATCCCCA AGGCGCGTGT AAAGGGGCTT

38401 AAGTGCCACC TGACGTCTAA GAAACCATT TATCATGAC ATTAACCTAT
TTCACGGTGG ACTGCAGATT CTTTGGTAAT AATAGTACTG TAATTGGATA

38451 AAAAATAGGC GTATCACGAG GCCCTTTCGT CTTCAAGAAT TGGATCCGAA
TTTTTATCCG CATAGTGCTC CGGGAAAGCA GAAGTTCTTA ACCTAGGCTT

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38501 TTCTTAATTT CTTAATTAA (SEQ ID NO:32)
AAGAATTAAA GAATTAATT (SEQ ID NO:33)

Figure 26 A0

1 CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG
GTAGTAGTTA TTATATGGAA TAAAACCTAA CTCGGTTAT ACTATTACTC

51 GGGGTGGAGT TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG
CCCCACCTCA AACACTGCAC CGCGCCCCGC ACCCTTGCCC CGCCCACTGC

101 TAGTAGTGTG GCGGAAGTGT GATGTTGCAA GTGTGGCGGA ACACATGTAA
ATCATCACAC CGCCTTCACA CTACAACGTT CACACCGCCT TGTGTACATT

151 GCGACGGATG TGGCAAAAGT GACGTTTTTG GTGTGCGCCG GTGTACACAG
CGCTGCCTAC ACCGTTTTCA CTGCAAAAAC CACACGCGGC CACATGTGTC

201 GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG TAAATTTGGG
CTTCACTGTT AAAAGCGCGC CAAAATCCGC CTACAACATC ATTTAAACCC

251 CGTAACCGAG TAAGATTGCG CCATTTTCGC GGGAAACTG AATAAGAGGA
GCATTGGCTC ATTCTAAACC GGTAAAAGCG CCCTTTTGAC TTATTCTCCT

301 AGTGAAATCT GAATAATTTT GTGTTACTCA TAGCGCGTAA TATTTGTCTA
TCACTTTAGA CTTATTAAAA CACAATGAGT ATCGCGCATT ATAAACAGAT

351 GGGCGCGGG GACTTTGACC GTTTACGTGG AGACTCGCCC AGGTGTTTTT
CCCCGCGCCC CTGAAACTGG CAAATGCACC TCTGAGCGGG TCCACAAAAA

401 CTCAGGTGTT TTCCGCGTTC CGGGTCAAAG TTGGCGTTTT ATTATTATAG
GAGTCCACAA AAGGCGCAAG GCCCAGTTTC AACCGCAAAA TAATAATATC

451 GCGGCCGCGA TCCATTGCAT ACGTTGTATC CATATCATAA TATGTACATT
CGCCGCGGCT AGGTAACGTA TGCAACATAG GTATAGTATT ATACATGTAA

501 TATATTGGCT CATGTCCAAC ATTACCGCCA TGTTGACATT GATTATTGAC
ATATAACCGA GTACAGGTG TAATGGCGGT ACAACTGTAA CTAATAACTG

551 TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA
ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT

601 TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG
ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC

651 CCCAACGACC CCCGCCCATT GACGTCAATA ATGACGTATG TTCCCATAGT
GGGTTGCTGG GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA

701 AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT
TTGCGGTTAT CCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

751 AAAGTCCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTACGCCC
TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCATGCGGG

801 CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCAGTA
GGATAACTGC AGTTACTGCC ATTTACCGGG CGGACCGTAA TACGGGTCAT

Figure 27A

901 TCGCTATTAC CATGGTGATG CGGTTTGGC AGTACATCAA TGGGCGTGGA
AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

951 TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA
ATCGCCAAAC TGAGTGCCCC TAAAGGTCA GAGGTGGGGT AACTGCAGTT

1001 TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA
ACCCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

1051 ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG
TGTTGAGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

1101 GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG
CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1151 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC
GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTGCG

1201 TCCGCGGCCG GGAACGGTGC ATTGGAACGC GGATTTCCCG TGCCAAGAGT
AGGCGCCGCG CCTTGCCACG TAACCTTGCG CCTAAGGGGC ACGGTTCTCA

1251 GAGATCTGCC ACCATGGCCG GCAAGTGGTC CAAGAGGTCC GTGCCCCGCT
CTCTAGACGG TGGTACCGGC CGTTCACCAG GTTCTCCAGG CACGGGCCGA

1301 GGTCCACCGT GAGGGAGAGG ATGAGGAGGG CCGAGCCCGC CGCCGACAGG
CCAGGTGGCA CTCCCTCTCC TACTCCTCCC GGCTCGGGCG GCGGCTGTCC

1351 GTGAGGAGGA CCGAGCCCGC CGCAGTGGGC GTGGGCGCCG TGTCCAGGGA
CACTCCTCCT GGCTCGGGCG GCGTCACCCG CACCCGCGGC ACAGGTCCCT

1401 CCTGGAGAAG CACGGCGCCA TCACCTCCTC CAACACCGCC GCCACCAACG
GGACCTCTTC GTGCCGCGGT AGTGGAGGAG GTTGTEGCGG CGGTGTTGC

1451 CCGACTGCGC CTGGCTGGAG GCCCAGGAGG ACGAGGAGGT GGGCTTCCCC
GGCTGACGCG GACCGACCTC CGGGTCTCTC TGCTCTCTCA CCCGAAGGGG

1501 GTGAGGCCCC AGGTGCCCCCT GAGGCCCATG ACCTACAAGG GCGCCGTGGA
CACTCCGGGG TCCACGGGGA CTCCGGGTAC TGGATGTTCC CGCGGCACCT

1551 CCTGTCCCAC TTCCTGAAGG AGAAGGGCGG CCTGGAGGGC CTGATCCACT
GGACAGGGTG AAGGACTTCC TCTTCCCGCC GGACCTCCCG GACTAGGTGA

1601 CCCAGAAGAG GCAGGACATC CTGGACCTGT GGGTGTACCA CACCCAGGGC
GGGTCTTCTC CGTCTGTAG GACCTGGACA CCCACATGGT GTGGGTCCCC

1651 TACTTCCCCG ACTGGCAGAA CTACACCCCC GGCCCCGCA TCAGGTTCCT
ATGAAGGGGC TGACCGTCTT GATGTGGGGG CCGGGGCCGT AGTCCAAGGG

1701 CCTGACCTTC GGCTGGTGCT TCAAGCTGGT GCCCGTGGAG CCCGAGAAGG
GGACTGGAAG CCGACCACGA AGTTCGACCA CGGGCACCTC GGGCTCTTCC

1751 TGGAGGAGGC CAACGAGGGC GAGAACAAC TCGCCGCCCA CCCCATGTCC
ACCTCCTCCG GTTGCTCCCG CTCTTGTTGA CGCGGCGGGT GGGGTACAGG

Figure 27B

1851 CTCCAAGCTG GCCTTCCACC ACGTGGCCAG GGAGCTGCAC CCCGAGTACT
GAGGTTTCGAC CGGAAGGTGG TGCACCGGTC CCTCGACGTG GGGCTCATGA

1901 ACAAGGACTG CTAAAGCCCG GGCAGATCTG CTGTGCCTTC TAGTTGCCAG
TGTTCCTGAC GATTTCGGGC CCGTCTAGAC GACACGGAAG ATCAACGGTC

1951 CCATCTGTTG TTTGCCCTC CCCCCTGCCT TCCTTGACCC TGAAGGTGC
GGTAGACAAC AAACGGGGAG GGGGCACGGA AGGAACTGGG ACCTTCCACG

2001 CACTCCCCTG GTCCTTTCCT AATAAAATGA GGAAATTGCA TCGCATTGTC
GTGAGGGTGA CAGGAAAGGA TTATTTTACT CCTTTAACGT AGCGTAACAG

2051 TGAGTAGGTG TCATTCTATT CTGGGGGGTG GGGTGGGGCA GGACAGCAAG
ACTCATCCAC AGTAAGATAA GACCCCCAC CCCACCCCGT CCTGTCGTTC

2101 GGGGAGGATT GGAAGACAA TAGCAGGCAT GCTGGGGATG CGGTGGGCTC
CCCCCTCTAA CCCTTCTGTT ATCGTCCGTA CGACCCCTAC GCCACCCGAG

2151 TATGGCCGAT CGGCGCGCCG TACTGAAATG TGTGGGCGTG GCTTAAGGGT
ATACCGGCTA GCGCGCGGCG ATGACTTTAC ACACCCGCAC CGAATTCCCA

2201 GGGAAAGAAT ATATAAGGTG GGGGTCTTAT GTAGTTTGT ATCTGTTTTG
CCCTTTCTTA TATATTCCAC CCCAGAATA CATCAAAACA TAGACAAAC

2251 CAGCAGCCGC CGCCGCCATG AGCACCAACT CGTTTGATGG AAGCATTGTG
GTCGTCGGCG GCGGCGGTAC TCGTGGTTGA GCAAACCTACC TTCGTAACAC

2301 AGCTCATATT TGACAACGCG CATGCCCCCA TGGGCCGGGG TCGTCAGAA
TCGAGTATAA ACTGTTGCGC GTACGGGGGT ACCCGGCCCC ACGCAGTCTT

2351 TGTGATGGGC TCCAGCATTG ATGGTCGCCC CGTCCTGCCC GCAAACCTCTA
ACACTACCCG AGGTGCTAAC TACCAGCGGG GCAGGACGGG CGTTTGAGAT

2401 CTACCTTGAC CTACGAGACC GTGTCTGGAA CGCCGTTGGA GACTGCAGCC
GATGGAACCTG GATGCTCTGG CACAGACCTT GCGGCAACCT CTGACGTCGG

2451 TCCGCCGCCG CTTAGCCGC TGCAGCCACC GCGCGCGGGA TTGTGACTGA
AGGCGGCGGC GAAGTCGGCG ACGTCGGTGG CGGGCGCCCT AACACTGACT

2501 CTTTGCTTTC CTGAGCCCGC TTGCAAACAG TGCAGCTTCC CGTTCATCCG
GAAACGAAAG GACTCGGGCG AACGTTTGTC ACGTCGAAGG GCAAGTAGGC

2551 CCCGCGATGA CAAGTTGACG GCTCTTTTGG CACAATTGGA TTCTTTGACC
GGGCGCTACT GTTCAACTGC CGAGAAAACC GTGTAACTT AAGAAACTGG

2601 CGGGAACCTA ATGTCGTTTC TCAGCAGCTG TTGGATCTGC GCCAGCAGGT
GCCCTTGAAT TACAGCAAAG AGTCGTCGAC AACCTAGACG CGGTCGTCCA

2651 TTCTGCCCTG AAGGCTTCCT CCCCTCCCAA TGCGGTTTAA AACATAAATA
AAGACGGGAC TTCCGAAGGA GGGGAGGGTT ACGCCAAATT TTGTATTTAT

2701 AAAAACCAGA CTCTGTTTGG ATTTGGATCA AGCAAGTGTC TTGCTGTCTT
TTTTTGGTCT GAGACAAACC TAAACCTAGT TCGTTCACAG AACGACAGAA

Figure 27C

2751 TATTTAGGGG TTTTGCGCGC GCGGTAGGCC CGGGACCAGC GGTCTCGGTC
ATAAATCCCC AAAACGCGCG CGCCATCCGG GCCCTGGTCG CCAGAGCCAG

2801 GTTGAGGGTC CTGTGTATTT TTTCCAGGAC GTGGTAAAGG TGACTCTGGA
CAACTCCCAG GACACATAAA AAAGGTCCTG CACCATTTC ACTGAGACCT

2851 TGTTCAGATA CATGGGCATA AGCCCGTCTC TGGGGTGGAG GTAGCACCAC
ACAAGTCTAT GTACCCGTAT TCGGGCAGAG ACCCCACCTC CATCGTGGTG

2901 TGCAGAGCTT CATGCTGCGG GGTGGTGTGG TAGATGATCC AGTCGTAGCA
ACGTCTCGAA GTACGACGCC CCACCACAAC ATCTACTAGG TCAGCATCGT

2951 GGAGCGCTGG GCGTGGTGCC TAAAAATGTC TTTCAGTAGC AAGCTGATTG
CCTCGCGACC CGCACCACGG ATTTTACAG AAAGTCATCG TTCGACTAAC

3001 CCAGGGGCAG GCCCTTGGTG TAAGTGTTTA CAAAGCGGTT AAGCTGGGAT
GGTCCCCGTC CGGGAACCAC ATTCACAAAT GTTTCGCCAA TTCGACCCTA

3051 GGGTGCATAC GTGGGGATAT GAGATGCATC TTGGACTGTA TTTTtaggTT
CCCACGTATG CACCCCTATA CTCTACGTAG AACCTGACAT AAAAATCCAA

3101 GGCTATGTTT CCAGCCATAT CCCTCCGGGG ATTCATGTTG TGCAGAACCA
CCGATACAAG GGTCCGTATA GGGAGGCCCC TAAGTACAAC ACGTCTTGGT

3151 CCAGCACAGT GTATCCGGTG CACTTGGGAA ATTTGTATG TAGCTTAGAA
GGTCGTGTCA CATAGGCCAC GTGAACCCTT TAAACAGTAC ATCGAATCTT

3201 GGAAATGCGT GGAAGAACTT GGAGACGCCC TTGTGACCTC CAAGATTTTC
CCTTTACGCA CCTTCTTGAA CCTCTGCGGG AACACTGGAG GTTCTAAAAG

3251 CATGCATTCTG TCCATAATGA TGGCAATGGG CCCACGGGCG GCGGCCTGGG
GTACGTAAAGC AGGTATTACT ACCGTTACCC GGGTGCCCGC CGCCGGACCC

3301 CGAAGATATT TCTGGGATCA CTAACGTCAT AGTTGTGTTT CAGGATGAGA
GCTTCTATAA AGACCCTAGT GATTGCAGTA TCAACACAAG GTCTTACTCT

3351 TCGTCATAGG CCATTTTAC AAAGCGCGGG CGGAGGGTGC CAGACTGCGG
AGCAGTATCC GGTAAAAATG TTTCGCGCCC GCCTCCACG GTCTGACGCC

3401 TATAATGGTT CCATCCGGCC CAGGGGCGTA GTTACCCTCA CAGATTTGCA
ATATTACCAA GGTAGGCCGG GTCCCCGCAT CAATGGGAGT GTCTAAACGT

3451 TTTCCACGCG TTTGAGTTCA GATGGGGGGA TCATGTCTAC CTGCGGGGCG
AAAGGGTGCG AAACCTCAAGT CTACCCCCCT AGTACAGATG GACGCCCCGC

3501 ATGAAGAAAA CGGTTTCCGG GGTAGGGGAG ATCAGCTGGG AAGAAAGCAG
TACTTCTTTT GCCAAAGGCC CCATCCCTC TAGTCGACCC TTCTTTCGTC

3551 GTTCCTGAGC AGCTGCGACT TACCGCAGCC GGTGGGCCCCG TAAATCACAC
CAAGGACTCG TCGACGCTGA ATGGCGTCGG CCACCCGGGC ATTTAGTGTG

3601 CTATTACCGG CTGCAACTGG TAGTTAAGAG AGCTGCAGCT GCCGTATCC
GATAATGGCC GACGTTGACC ATCAATTCTC TCGACGTCGA CGGCAGTAGG

3651 CTGAGCAGGG GGGCCACTTC GTTAAGCATG TCCCTGACTC GCATGTTTTT
GACTCGTCCC CCCGGTGAAG CAATTCGTAC AGGGACTGAG CGTACAAAAG

Figure 27D

3701 CCTGACCAAA TCCGCCAGAA GGCGCTCGCC GCCCAGCGAT AGCAGTTCTT
GGACTGGTTT AGGCGGTCTT CCGCGAGCGG CGGGTCGCTA TCGTCAAGAA

3751 GCAAGGAAGC AAAGTTTTTC AACGGTTTGA GACCGTCCGC CGTAGGCATG
CGTTCCTTCG TTCAAAAAG TTGCCAAACT CTGGCAGGCG GCATCCGTAC

3801 CTTTGTAGCG TTTGACCAAG CAGTTCCAGG CGGTCCCACA GCTCGGTCAC
GAAAACTCGC AAAGTGGTTC GTCAAGGTCC GCCAGGGTGT CGAGCCAGTG

3851 CTGCTCTACG GCATCTCGAT CCAGCATATC TCCTCGTTTC GCGGGTTGGG
GACGAGATGC CGTAGAGCTA GGTCTGTATG AGGAGCAAAG CGCCCAACCC

3901 GCGGCTTTCG CTGTACGGCA GTAGTCGGTG CTCGTCCAGA CGGGCCAGGG
CGCCGAAAGC GACATGCCGT CATCAGCCAC GAGCAGGTCT GCCCGGTCCC

3951 TCATGTCTTT CCACGGGCGC AGGGTCTCTG TCAGCGTAGT CTGGGTCACG
AGTACAGAAA GGTGCCCGCG TCCCAGGAGC AGTCGCATCA GACCCAGTGC

4001 GTGAAGGGGT GCGCTCCGGG CTGCGCGCTG GCCAGGGTGC GCTTGAGGCT
CACTTCCCCA CGCGAGGCCG GACGCGCGAC CGGTCCCACG CGAACTCCGA

4051 GGTCTGTCTG GTGCTGAAGC GCTGCCGGTC TTCGCCCTGC GCGTCGGCCA
CCAGGACGAC CACGACTTCG CGACGGCCAG AAGCGGGACG CGCAGCCGGT

4101 GGTAGCATTT GACCATGGTG TCATAGTCCA GCCCCTCCGC GCGTGGGCC
CCATCGTAAA CTGGTACCAC AGTATCAGGT CGGGGAGGCG CCGCACCGGG

4151 TTGGCGCGCA GCTTGCCCTT GGAGGAGGCG CCGCACGAGG GGCAGTGCAG
AACC CGCGCT CGAACGGGAA CCTCCTCCGC GGCCTGCTCC CCGTCACGTC

4201 ACTTTTGAGG GCGTAGAGCT TGGGCGCGAG AAATACCGAT TCCGGGGAGT
TGAAAACCTC CGCATCTCGA ACCCGCGCTC TTTATGGCTA AGGCCCTCA

4251 AGGCATCCGC GCCGCAGGCC CCGCAGACGG TCTCGCATTG CACGAGCCAG
TCCGTAGGCG CGGCGTCCGG GGCCTCTGCC AGAGCGTAAG GTGCTCGGTC

4301 GTGAGCTCTG GCGTTCGGG GTCAAAAACC AGGTTTCCCC CATGCTTTTT
CACTCGAGAC CGGCAAGCCC CAGTTTTTGG TCCAAAGGGG GTACGAAAAA

4351 GATGCGTTTC TTACCTCTGG TTTCCATGAG CCGGTGTCCA CGCTCGGTGA
CTACGCAAAG AATGGAGACC AAAGGTACTC GGCCACAGGT GCGAGCCACT

4401 CGAAAAGGCT GTCCGTGTCC CCGTATACAG ACTTGAGAGG CCTGTCTCG
GCTTTTCCGA CAGGCACAGG GGCATATGTC TGAACCTCTC GGACAGGAGC

4451 AGCGGTGTTC CGCGGTCTCT CTCGTATAGA AACTCGGACC ACTCTGAGAC
TCGCCACAAG GCGCCAGGAG GAGCATATCT TTGAGCCTGG TGAGACTCTG

4501 AAAGGCTCGC GTCCAGGCCA GCACGAAGGA GGCTAAGTGG GAGGGGTAGC
TTTCCGAGCG CAGGTCCGGT CGTGCTTCCT CCGATTCAAC CTCCCCATCG

4551 GGTCTGTGTC CACTAGGGGG TCCACTCGCT CCAGGGTGTG AAGACACATG
CCAGCAACAG GTGATCCCCC AGGTGAGCGA GGTCCCACAC TTCTGTGTAC

4601 TCGCCCTCTT CGGCATCAAG GAAGGTGATT GGTGTGTAGG TGTAGGCCAC
AGCGGGAGAA GCCGTAGTTC CTTCCACTAA CCAAACATCC ACATCCGGTG

Figure 27E

4701 CGTCCTCACT CTCTTCCGCA TCGCTGTCTG CGAGGGCCAG CTGTTGGGGT
GCAGGAGTGA GAGAAGGCGT AGCGACAGAC GCTCCCGGTC GACAACCCCA

4751 GAGTACTCCC TCTGAAAAGC GGGCATGACT TCTGCGCTAA GATTGTCACT
CTCATGAGGG AGACTTTTCG CCCGTACTGA AGACGCGATT CTAACAGTCA

4801 TTCCAAAAAC GAGGAGGATT TGATATTAC CTGCCCCGCG GTGATGCCTT
AAGGTTTTTG CTCTCCTAA ACTATAAGTG GACCGGGCGC CACTACGGAA

4851 TGAGGGTGGC CGCATCCATC TGGTCAGAAA AGACAATCTT TTTGTTGTCA
ACTCCACCG GCGTAGGTAG ACCAGTCTT TCTGTTAGAA AAACAACAGT

4901 AGCTTGGTGG CAAACGACCC GTAGAGGGCG TTGGACAGCA ACTTGGCGAT
TCGAACCACC GTTTGCTGGG CATCTCCCGC AACCTGTCGT TGAACCGCTA

4951 GGAGCGCAGG GTTTGGTTTT TGTCGCGATC GGCGCGCTCC TTGGCCGCGA
CCTCGCGTCC CAAACCAAAA ACAGCGCTAG CCGCGCGAGG AACCGGCGCT

5001 TGTTTAGCTG CACGTATTCTG CGCGCAACGC ACCGCCATTC GGGAAAGACG
ACAAATCGAC GTGCATAAGC GCGCGTTGCG TGGCGGTAAG CCCTTCTGTC

5051 GTGGTGGCT CGTCGGGCAC CAGGTGCACG CGCCAACCGC GGTGTGTGACG
CACCACGCGA GCAGCCCGTG GTCCACGTGC GCGGTTGGCG CCAACACGTC

5101 GGTGACAAGG TCAACGCTGG TGGCTACCTC TCCGCGTAGG CGCTCGTTGG
CCTGTTCC AGTTGCGACC ACCGATGGAG AGGCGCATCC GCGAGCAACC

5151 TCCAGCAGAG GCGGCCGCCC TTGCGCGAGC AGAATGGCGG TAGGGGGTCT
AGGTGCTCTC CGCCGGCGGG AACGCGCTCG TCTTACCGCC ATCCCCAGA

5201 AGCTGCGTCT CGTCCGGGG GTCTGCGTCC ACGGTAAAGA CCCCCGGCAG
TCGACGAGA GCAGGCCCC CAGACGAGG TGCCATTTCT GGGGCCCCGTC

5251 CAGGCGCGCG TCGAAGTAGT CTATCTGCA TCCTTGCAAG TCTAGCGCCT
GTCGCGCGC AGCTTCATCA GATAGAACGT AGGAACGTT AGATCGCGGA

5301 GCTGCCATGC GCGGGCGGCA AGCGCGCGCT CGTATGGGTT GAGTGGGGGA
CGACGGTACG CGCCCGCCGT TCGCGCGCGA GCATACCAA CTCACCCCT

5351 CCCCATGGCA TGGGGTGGGT GAGCGCGGAG GCGTACATGC CGCAAATGTC
GGGGTACCGT ACCCCACCCA CTCGCGCTC CGCATGTACG GCGTTTACAG

5401 GTAAACGTAG AGGGGCTCTC TGAGTATTCC AAGATATGTA GGGTAGCATC
CATTTGCATC TCCCCGAGAG ACTCATAAGG TTCTATACAT CCCATCGTAG

5451 TTCCACCGCG GATGCTGGCG CGCACGTAAT CGTATAGTTC GTGCGAGGGA
AAGGTGGCGC CTACGACCGC GCGTGCATTA GCATATCAAG CACGCTCCCT

5501 GCGAGGAGGT CGGGACCGAG GTTGCTACGG GCGGGCTGCT CTGCTCGGAA
CGCTCCTCCA GCCCTGGCTC CAACGATGCC CGCCCGACGA GACGAGCCTT

5551 GACTATCTGC CTGAAGATGG CATGTGAGTT GGATGATATG GTTGACGCT
CTGATAGACG GACTTCTACC GTACACTCAA CCTACTATAC CAACCTGCGA

Figure 27F

5651 GAGGCGTAGG AGTCGCGCAG CTTGTTGACC AGCTCGGCGG TGACCTGCAC
CTCCGCATCC TCAGCGCGTC GAACAACTGG TCGAGCCGCC ACTGGACGTG

5701 GTCTAGGGCG CAGTAGTCCA GGGTTTCCTT GATGATGTCA TACTTATCCT
CAGATCCCGC GTCATCAGGT CCCAAAGGAA CTACTACAGT ATGAATAGGA

5751 GTCCCTTTTT TTTCCACAGC TCGCGGTTGA GGACAACTC TTCGCGGTCT
CAGGGAAAAA AAAGGTGTCT AGCGCCAACCT CCTGTTTGAG AAGCGCCAGA

5801 TTCCAGTACT CTTGGATCGG AAACCCGTCG GCCTCCGAAC GGTAAGAGCC
AAGGTCATGA GAACCTAGCC TTTGGGCAGC CGGAGGCTTG CCATTCTCGG

5851 TAGCATGTAG AACTGGTTGA CGGCCTGGTA GGCGCAGCAT CCCTTTTCTA
ATCGTACATC TTGACCAACT GCCGGACCAT CCGCGTCGTA GGGAAAAGAT

5901 CGGGTAGCGC GTATGCCTGC GCGGCCTTCC GGAGCGAGGT GTGGGTGAGC
GCCCATCGCG CATA CGGACG CGCCGGAAGG CCTCGCTCCA CACCCACTCG

5951 GCAAAGGTGT CCCTGACCAT GACTTTGAGG TACTGGTATT TGAAGTCAGT
CSTTTCCACA GGGACTGGTA CTGAACTCC ATGACCATAA ACTTCAGTCA

6001 GTCGTCGCAT CCGCCCTGCT CCCAGAGCAA AAAGTCCGTG CGCTTTTGG
CAGCAGCGTA GCGGGGACGA GGGTCTCGTT TTTCAGGCAC GCGAAAAACC

6051 AACGCGGATT TGGCAGGGCG AAGGTGACAT CGTTGAAGAG TATCTTTCCC
TTGCGCCTAA ACCGTCCCGC TTCCACTGTA GCAACTTCTC ATAGAAAGGG

6101 GCGCGAGGCA TAAAGTTGCG TGTGATGCGG AAGGGTCCCG GCACCTCGGA
CGCGCTCCGT ATTTCAACGC AACTACGCC TTCCCAGGGC CGTGGAGCCT

6151 ACGGTTGTTA ATTACCTGGG CGGCGAGCAC GATCTCGTCA AAGCCGTGTA
TGCCAACAAT TAATGGACCC GCCGCTCGTG CTAGAGCAGT TTCGGCAACT

6201 TGTGTGGCC CACAATGTAA AGTTCCAAGA AGCGCGGGAT GCCCTTGATG
ACAACACCGG GTGTTACATT TCAAGGTTCT TCGCGCCCTA CGGGAACCTAC

6251 GAAGGCAATT TTTTAAGTTC CTCGTAGGTG AGCTCTTCAG GGGAGCTGAG
CTTLCGTAA AAAATTCAAG GAGCATCCAC TCGAGAAGTC CCCTCGACTC

6301 CCCGTGCTCT GAAAGGGCCC AGTCTGCAAG ATGAGGGTTG GAAGCGACGA
GGGCACGAGA CTTTCCCGG TCAGACGTTT TACTCCCAAC CTTGCTGCT

6351 ATGAGCTCCA CAGGTCACGG GCCATTAGCA TTTGCAGGTG GTCGCGAAAG
TACTCGAGGT GTCCAGTGCC CGGTAATCGT AAACGTCCAC CAGCGCTTTC

6401 GTCCTAAACT GGCGACCTAT GGCCATTTT TCTGGGGTGA TGCAGTAGAA
CAGGATTTGA CCGCTGGATA CCGGTAAAA AGACCCCACT ACGTCATCTT

6451 GGTAAGCGGG TCTTGTTCCT AGCGGTCCCA TCCAAGGTTT GCGGCTAGGT
CCATTCGCCC AGAACAAGGG TCGCCAGGTT AGGTTCCAAG CGCCGATCCA

6501 CTCGCGCGGC AGTCACTAGA GGCTCATCTC CGCCGAACCT CATGACCAGC
GAGCGCGCCG TCAGTGATCT CCGAGTAGAG GCGGCTTGAA GTACTGGTGC

Figure 27G

6601 TACATCGTAG GTGACAAAGA GACGCTCGGT GCGAGGATGC GAGCCGATCG
ATGTAGCATC CACTGTTTCT CTGCGAGCCA CGCTCCTACG CTCGGCTAGC

6651 GGAAGAACTG GATCTCCCGC CACCAATTGG AGGAGTGGCT ATTGATGTGG
CCTTCTTGAC CTAGAGGGCG GTGGTTAACC TCCTCACC GA TAACTACACC

6701 TGAAAGTAGA AGTCCCTGCG ACGGGCCGAA CACTCGTGCT GGCTTTTGTA
ACTTTCATCT TCAGGGACGC TGCCCGGCTT GTGAGCACGA CCGAAAACAT

6751 AAAACGTGCG CAGTACTGGC AGCGGTGCAC GGGCTGTACA TCCTGCACGA
TTTTGCACGC GTCATGACCG TCGCCACGTG CCCGACATGT AGGACGTGCT

6801 GGTTGACCTG ACGACCGCGC ACAAGGAAGC AGAGTGGGAA TTTGAGCCCC
CCAACTGGAC TGCTGGCGCG GTTCTCTTCG TCTCACCTT AACTCGGGG

6851 TCGCCTGGCG GGTTCGGCTG GTGGTCTTCT ACTTCGGCTG CTTGTCCTTG
AGCGGACCGC CCAAACCGAC CACCAGAAGA TGAAGCCGAC GAACAGGAAC

6901 ACCGTCTGGC TGCTCGAGGG GAGTTACGGT GGATCGGACC ACCACGCCGC
TGGCAGACCG ACGAGCTCCC CTCAATGCCA CCTAGCCTCG TGGTGCGGCG

6951 GCGAGCCCAA AGTCCAGATG TCCGCGCGCG GCGGTCGGAG CTTGATGACA
CGCTCGGGTT TCAGGTCTAC AGGCGCGCGC CGCCAGCCTC GAACTACTGT

7001 ACATCGCGCA GATGGGAGCT GTCCATGGTC TGGAGCTCCC GCGGCGTCAG
TGTCGCGGT CTACCTCGA CAGGTACCAG ACCTCGAGGG CGCCGCAGTC

7051 GTCAGGCGGG AGCTCCTGCA GGTTTACCTC GCATAGACGG GTCAGGGCGC
CAGTCCGCCC TCGAGGACGT CCAAATGGAG CGTATCTGCC CAGTCCCGCG

7101 GGGCTAGATC CAGGTGATAC CTAATTTCCA GGGGCTGGTT GGTGGCGGGC
CCCGATCTAG GTCCACTATG GATTAAAGGT CCCCACCAA CCACCGCCG

7151 TCGATGGCTT GCAAGAGGCC GCATCCCCGC GCGCGACTA CGGTACCGCG
AGCTACCGAA CGTTCTCCGG CGTAGGGGCG CCGCGCTGAT GCCATGGCGC

7201 CGGCGGGCGG TGGGCCGCGG GGGTGTCTT GGATGATGCA TCTAAAAGCG
GCCGCCGCC ACCCGCGGCC CCCACAGGAA CCTACTACGT AGATTTTCGC

7251 GTGACGCGGG CGAGCCCCCG GAGGTAGGGG GGGCTCCGGA CCCGCCGGGA
CACTGCGCCC GCTCGGGGGC CTCCATCCCC CCCGAGGCTT GGGCGGCCCT

7301 GAGGGGGCAG GGGCACGTCG GCGCCGCGCG CGGGCAGGAG CTGGTGCTGC
CTCCCCCGTC CCCGTGCAGC CGCGGCGCGC GCGGCTCTC GACCACGACG

7351 GCGCGTAGGT TGCTGGCGAA CGCGACGACG CGGCGGTTGA TCTCCTGAAT
CGCGCATCCA ACGACCGCTT CGCTGCTGC GCCGCCAAT AGAGGACTTA

7401 CTGGCGCCTC TGCGTGAAGA CGACGGGCCC GGTGAGCTTG AACCTGAAAG
GACCGCGGAG ACGCACTTCT GCTGCCCGG CCACTCGAAC TTGGACTTTC

7451 AGAGTTCGAC AGAATCAATT TCGGTGTCGT TGACGGCGGC CTGGCGCAAA
TCTCAAGCTG TCTTAGTTAA AGCCACAGCA ACTGCCGCCG GACCGCGTTT

Figure 27H

7551 CTGCTCGATC TCTTCCTCCT GGAGATCTCC GCGTCCGGCT CGCTCCACGG
GACGAGCTAG AGAAGGAGGA CCTCTAGAGG CGCAGGCCGA GCGAGGTGCC

7601 TGGCGGCGAG GTCGTTGGAA ATGCGGGCCA TGAGCTGCCA GAAGGCGTTG
ACCGCCGCTC CAGCAACCTT TACGCCCGGT ACTCGACGCT CTTCCGCAAC

7651 AGGCCTCCCT CGTTCCAGAC GCGGCTGTAG ACCACGCCCC CTTCCGGCATC
TCCGGAGGGA GCAAGGTCTG CGCCGACATC TGGTGCGGGG GAAGCCGTAG

7701 GCGGGCGCGC ATGACCACCT GCGCGAGATT GAGCTCCACG TGCCGGGCGA
CGCCCGCGCG TACTGGTGA CGCGCTCTAA CTCGAGGTGC ACGGCCCGCT

7751 AGACGGCGTA GTTTCGCAGG CGCTGAAAGA GGTAGTTGAG GGTGGTGGCG
TCTGCCGCAT CAAAGCGTCC GCGACTTTCT CCATCAACTC CCACCACCGC

7801 GTGTGTTCTG CCACGAAGAA GTACATAACC CAGCGTCGCA ACGTGGATTG
CACACAAGAC GGTGCTTCTT CATGTATTGG GTCGCAGCGT TGCACCTAAG

7851 GTTGATATCC CCCAAGGCCT CAAGGCGCTC CATGGCCTCG TAGAAGTCCA
CAACTATAGG GGGTTCCGGA GTTCCGCGAG GTACCGGAGC ATCTTCAGGT

7901 CGGCGAAGTT GAAAACTGG GAGTTGCGCG CCGACACGGT TAACTCCTCC
GCCGCTTCAA CTTTTTGACC CTCAACGCGC GGCTGTGCCA ATTGAGGAGG

7951 TCCAGAAGAC GGATGAGCTC GGCGACAGTG TCGCGCACCT CGCGCTCAAA
AGGTCTTCTG CCTACTCGAG CCGCTGTCAC AGCGCGTGGA GCGCGAGTTT

8001 GGCTACAGGG GCCTCTTCTT CTTCTTCAAT CTCCTCTTCC ATAAGGGCCT
CCGATGTCCC CGGAGAAGAA GAAGAAGTTA GAGGAGAAGG TATTTCCGGA

8051 CCCCTTCTTC TTCTTCTGGC GCGGGTGGGG GAGGGGGGAC ACGGCGGCGA
GGGAAGAAG AAGAAGACCG CCGCCACCCC CTCCTCCCTG TGCCGCGCT

8101 CGACGGCGCA CCGGGAGGCG GTCGACAAAG CGCTCGATCA TCTCCCCGCG
GCTGCCGCGT GGCCCTCCGC CAGCTGTTTC GCGAGCTAGT AGAGGGGCGC

8151 GCGACGGCGC ATGGTCTCGG TGACGGGCGG GCCGTCTCTG CGGGGGCGCA
CGCTGCCGCG TACCAGAGCC ACTGCCGCGC CGGCAAGAGC GCCCCCGCT

8201 GTTGGAAGAC GCCGCCCGTC ATGTCCCGGT TATGGGTTGG CGGGGGGCTG
CAACCTTCTG CGGCGGGCAG TACAGGGCCA ATACCAACC GCCCCCGAC

8251 CCATGCGGCA GGGATACGGC GCTAACGATG CATCTCAACA ATTGTTGTGT
GGTACGCCGT CCCTATGCCG CGATTGCTAC GTAGAGTTGT TAACAACACA

8301 AGGTACTCCG CCGCCGAGGG ACCTGAGCGA GTCCGCATCG ACCGGATCGG
TCCATGAGGC GCGGCTCCC TGGACTCGCT CAGGCGTAGC TGGCCTAGCC

8351 AAAACCTCTC GAGAAAGGCG TCTAACCAGT CACAGTCGCA AGGTAGGCTG
TTTTGGAGAG CTCTTTCCGC AGATTGGTCA GTGTCAGCGT TCCATCCGAC

8401 AGCACCGTGG CGGGCGGCAG CGGGCGGCGG TCGGGGTTGT TTCTGGCGGA
TCGTGGCACC GCGCGCGTC GCGCGCGCC AGCCCCAACA AAGACCGCCT

Figure 27I

8501 TCGACAGAAG CACCATGTCC TTGGGTCCGG CCTGCTGAAT GCGCAGGCGG
AGCTGTCTTC GTGGTACAGG AACCCAGGCC GGACGACTTA CGCGTCCGCC

8551 TCGGCCATGC CCCAGGCTTC GTTTTGACAT CGGCGCAGGT CTTTGTAGTA
AGCCGGTACG GGGTCCGAAG CAAAACGTGA GCCGCGTCCA GAAACATCAT

8601 GTCTTGCA TG AGCCTTTCTA CCGGCACTTC TTCTTCTCCT TCCTCTTGTC
CAGAACGTAC TCGGAAAGAT GGCCGTGAAG AAGAAGAGGA AGGAGAACAG

8651 CTGCATCTCT TGCATCTATC GCTGCGGCGG CGGCGGAGTT TGGCCGTAGG
GACGTAGAGA ACGTAGATAG CGACGCCGCC GCCGCCTCAA ACCGGCATCC

8701 TGGCGCCCTC TTCCTCCCAT GCGTGTGACC CCGAAGCCCC TCATCGGCTG
ACCGCGGGAG AAGGAGGGTA CGCACACTGG GGCTTCGGGG AGTAGCCGAC

8751 AAGCAGGGCT AGGTCCGGCA CAACGCGCTC GGCTAATATG GCCTGCTGCA
TTCGTCCCGA TCCAGCCGCT GTTGCGCGAG CCGATTATAC CGGACGACGT

8801 CCTGCGTGAG GGTAGACTGG AAGTCATCCA TGTCCACAAA GCGGTGGTAT
GGACGCACTC CCATCTGACC TTCAGTAGGT ACAGGTGTTT CGCCACCATA

8851 GCGCCCGTGT TGATGGTGTA AGTGCAAGTT GCCATAACGG ACCAGTTAAC
CGCGGGCACA ACTACCACAT TCACGTCAAC CGGTATTGCC TGGTCAATTG

8901 GSTCTGGTGA CCCGGCTGCG AGAGCTCGGT GTACCTGAGA CGCGAGTAAG
CCAGACCACT GGGCCGACGC TCTCGAGCCA CATGGACTCT GCGCTCATTC

8951 CCCTCGAGTC AAATACGTAG TCGTTGCAAG TCCGCACCAG GTACTGGTAT
GGGAGCTCAG TTTATGCATC AGCAACGTTT AGGCGTGGTC CATGACCATA

9001 CCCACCAAAA ACTGCGGCGG CGGCTGGCGG TAGAGGGGCC AGCGTAGGGT
GGGTGGTTTT TCACGCCGCC GCCGACGCC ATCTCCCCGG TCGCATCCCA

9051 GGCCGGGGCT CCGGGGGCGA GATCTTCCAA CATAAGGCGA TGATATCCGT
CCGGCCCCGA GGCCCCGCT CTAGAAGGTT GTATTCCGCT ACTATAGGCA

9101 AGATGTACCT GGACATCCAG GTGATGCCGG CGGCGGTGGT GGAGGCGCGC
TCTACATGGA CTTGTAGGTC CACTACGGCC GCCGCCACCA CCTCCGCGCG

9151 GGAAAGTCGC GGACGCGGTT CCAGATGTTG CGCAGCGGCA AAAAGTGCTC
CCTTTCAGCG CCTGCGCCAA GGTCTACAAC GCGTCGCCGT TTTTCACGAG

9201 CATGGTCGGG ACGCTCTGGC CGGTCAGGCG CGCGCAATCG TTGACGCTCT
GTACCAGCCC TCGGAGACCG GCCAGTCCGC GCGCGTTAGC AACTGCGAGA

9251 AGACCGTGCA AAAGGAGAGC CTGTAAGCGG GCACTCTTCC GTGGTCTGGT
TCTGGCACGT TTTCTCTCG GACATTCGCC CGTGAGAAGG CACCAGACCA

9301 GGATAAATTC GCAAGGGTAT CATGGCGGAC GACCGGGGTT CGAGCCCCGT
CCTATTAAAG CGTCCCATTA GTACCGCCTG CTGGCCCCAA GCTCGGGGCA

9351 ATCCGGCCGT CCGCCGTGAT CCATGCGGTT ACCGCCCGCG TGTCGAACCC
TAGGCCGGCA GGCGGCACTA GGTACGCCAA TGGCGGGCGC ACAGCTTGGG

Figure 27J

9451 GGC GCG GCG CTGCTGCGCT AGCTTTTTTG GCCACTGGCC GCGCGCAGCG
CCGCGCCGCC GACGACGCGA TCGAAAAAAC CCGTGACCGG CCGCGCTCGC

9501 TAAGCGGTTA GGCTGGAAAG CGAAAGCATT AAGTGGCTCG CTCCTGTAG
ATTGCCCAAT CCGACCTTTC GCTTTCGTAA TTCACCGAGC GAGGGACATC

9551 CCGGAGGGTT ATTTTCCAAG GGTGAGTCG CGGGACCCCC GTTCGAGTC
GGCCTCCCAA TAAAAGGTTC CCAACTCAGC GCCCTGGGGG CCAAGCTCAG

9601 TCGGACCGGC CGGACTGCGG CGAACGGGGG TTTGCCCTCC CGTCATGCAA
AGCCTGCGCG GCCTGACGCC GCTTGCCCCC AAACGGAGGG GCAGTACGTT

9651 GACCCCGCTT GCAAATTCCT CCGGAAACAG GGACGAGCCC CTTTTTTGCT
CTGGGGCGAA CGTTTAAGGA GGCTTTTGTC CCTGCTCGGG GAAAAAACGA

9701 TTTCCCAGAT GCATCCGGTG CTGCGGCAGA TGCGCCCCC TCCTCAGCAG
AAAGGTCTA CGTAGGCCAC GACGCCGTCT ACGCGGGGGG AGGAGTCGTC

9751 CGGCAAGAGC AAGAGCAGCG GCAGACATGC AGGGCACCCCT CCCTCCTCC
GCCGTTCTCG TTCTCGTCGC CGTCTGTACG TCCCGTGGGA GGGGAGGAGG

9801 TACCGCGTCA GGAGGGGCGA CATCCGCGGT TGACGCGGCA GCAGATGGTG
ATGGCGCAGT CCTCCCCGCT GTAGGCGCCA ACTGCGCCGT CGTCTACCAC

9851 ATTACGAACC CCCGCGGCGC CGGGCCCGGC ACTACCTGGA CTTGGAGGAG
TAATGCTTGG GGGCGCCGCG GCCCGGGCCG TGATGGACCT GAACCTCCTC

9901 GCGGAGGGCC TGGCGCGGCT AGGAGCGCCC TCTCCTGAGC GGCACCCAAG
CCGCTCCCGG ACCGCGCCGA TCCTCGCGGG AGAGGACTCG CCGTGGGTTT

9951 GGTGCAGCTG AAGCGTGATA CGCGTGAGGC GTACGTGCCG CGGCAGAACC
CCACGTCGAC TTCGCACTAT GCGCACTCCG CATGCACGGC GCCGTCTTGG

10001 TGTTTCGCGA CCGCGAGGGA GAGGAGCCCG AGGAGATGCG GGATCGAAAG
ACAAAGCGCT GCGCTCCCT CTCTCGGGC TCCTCTACGC CCTAGCTTTC

10051 TTCCACGCAG GCGCGAGCT GCGGCATGGC CTGAATCGCG AGCGGTTGCT
AAGGTGCGTC CCGCGCTCGA CGCCGTACCG GACTTAGCGC TCGCCAACGA

10101 GCGCGAGGAG GACTTTGAGC CCGACGCGCG AACC GGGATT AGTCCCGCGC
CGCGCTCCTC CTGAAACTCG GGCTGCGCGC TTGGCCCTAA TCAGGGCGCG

10151 GCGCACACGT GCGGCGCGCC GACCTGGTAA CCGCATACGA GCAGACGGTG
CGCGTGTGCA CCGCCGGCGG CTGGACCATT GGCGTATGCT CGTCTGCCAC

10201 AACCAGGAGA TTAAC TTCA AAAAGCTTT AACACCACG TGC GTACGCT
TTGGTCTCT AATTGAAAGT TTTTCGAAA TTGTTGGTGC ACGCATGCGA

10251 TGTGGCGCGC GAGGAGGTGG CTATAGGACT GATGCATCTG TGGGACTTTG
ACACCGCGCG CTCCTCCACC GATATCCTGA CTACGTAGAC ACCCTGAAAC

10301 TAAGCGCGCT GGAGCAAAAC CCAAATAGCA AGCCGCTCAT GGCGCAGCTG
ATTGCGCGCA CCTCGTTTTG GGTATATCGT TCGGCGAGTA CCGCGTCGAC

Figure 27K

10401 GCTAAACATA GTAGAGCCCG AGGGCCGCTG GCTGCTCGAT TTGATAAACA
CGATTTGTAT CATCTCGGGC TCCCGGCGAC CGACGAGCTA AACTATTTGT

10451 TCCTGCAGAG CATAGTGGTG CAGGAGCGCA GCTTGAGCCT GGCTGACAAG
AGGACGTCTC GTATCACCAC GTCCTCGCGT CGAACTCGGA CCGACTGTTT

10501 GTGGCCGCCA TCAACTATTC CATGCTTAGC CTGGGCAAGT TTTACGCCCC
CACC GGCGGT AGTTGATAAG GTACGAATCG GACCCGTTCA AAATGCGGGC

10551 CAAGATATAC CATACCCCTT ACGTTCCCAT AGACAAGGAG GTAAAGATCG
GTTCTATATG GTATGGGGAA TGCAAGGGTA TCTGTTCTC CATTTCTAGC

10601 AGGGGTTCTA CATGCGCATG GCGCTGAAGG TGCTTACCTT GAGCGACGAC
TCCCCAAGAT GTACGCGTAC CGCGACTTCC ACGAATGGAA CTCGCTGCTG

10651 CTGGGCGTTT ATCGCAACGA GCGCATCCAC AAGGCCGTGA GCGTGAGCCG
GACCCGCAAA TAGCGTTGCT CGCGTAGGTG TTCCGGCACT CGCACTCGGC

10701 GCGGCGCGAG CTCAGCGACC GCGAGCTGAT GCACAGCCTG CAAAGGGCCC
CGCCGCGCTC GAGTCGCTGG CGCTCGACTA CGTGTGCGAC GTTTCCCGG

10751 TGGCTGGCAC GGGCAGCGGC GATAGAGAGG CCGAGTCCTA CTTTGACGCG
ACCGACCGTG CCCGTCGCCG CTATCTCTCC GGCTCAGGAT GAAACTGCGC

10801 GGCGCTGACC TGCGCTGGGC CCCAAGCCGA CGCGCCCTGG AGGCAGCTGG
CCGCGACTGG ACGCGACCCG GGGTTCGGCT GCGCGGGACC TCCGTCGACC

10851 GGCCGGACCT GGGCTGGCGG TGGCACCCGC GCGCGCTGGC AACGTCGGCG
CCGGCCTGGA CCCGACCGCC ACCGTGGGCG CGCGCGACCG TTGCAGCCGC

10901 GCGTGAGGGA ATATGACGAG GACGATGAGT ACGAGCCAGA GGACGGCGAG
CGCACCTCCT TATACTGCTC CTGCTACTCA TGCTCGGTCT CCTGCCGCTC

10951 TACTAAGCGG TGATGTTTCT GATCAGATGA TGCAAGACGC AACGGACCCG
ATGATTGCC ACTACAAAGA CTAGTCTACT ACGTTCTGCG TTGCCTGGGC

11001 GCGGTGCGGG CGGCGCTGCA GAGCCAGCCG TCCGGCCTTA ACTCCACGGA
CGCCACGCCC GCCGCGACGT CTCGGTCGGC AGGCCGGAAT TGAGGTGCCT

11051 CGACTGGCGC CAGGTCATGG ACCGCATCAT GTCGCTGACT GCGCGCAATC
GCTGACCGCG GTCCAGTACC TGCCGTAGTA CAGCGACTGA CGCGCGTTAG

11101 CTGACGCGTT CCGGCAGCAG CCGCAGGCCA ACCGGCTCTC CGCAATTCTG
GACTGCGCAA GGCCGTCGTC GCGTCCGGT TGGCCGAGAG GCGTTAAGAC

11151 GAAGCGGTGG TCCCGGCGCG CGCAAACCCC ACGCACGAGA AGGTGCTGGC
CTTCGCCACC AGGGCCGCGC GCGTTTGGGG TGCGTGCTCT TCCACGACCG

11201 GATCGTAAAC GCGCTGGCCG AAAACAGGGC CATCCGGCCC GACGAGGCCG
CTAGCATTTG CGCGACCGGC TTTTGTCCCG GTAGGCCGGG CTGCTCCGGC

11251 GCCTGGTCTA CGACGCGCTG CTTAGCGCGG TGGCTCGTTA CAACAGCGGC
CGGACCAGAT GCTGCGCGAC GAAGTCGCGC ACCGAGCAAT GTTGTGCGCG

Figure 27L

11351 GGC GCAGCGT GAGCGCGCG AGCAGCAGGG CAACCTGGGC TCCATGGTTG
CCGCGTCGCA CTCGCGCGCG TCGTCGTCCC GTTGGACCCG AGGTACCAAC

11401 CACTAAACGC CTTCCTGAGT ACACAGCCCG CCAACGTGCC GCGGGGACAG
GTGATTGCG GAAGGACTCA TGTGTCGGGC GGTGACACGG CGCCCTGTCT

11451 GAGGACTACA CCAACTTTGT GAGCGCACTG CGGCTAATGG TGACTGAGAC
CTCCTGATGT GGTGAAACA CTCGCGTGAC GCCGATTACC ACTGACTCTG

11501 ACCGCAAAGT GAGGTGTACC AGTCTGGGCC AGACTATTTT TTCCAGACCA
TGGCGTTTCA CTCACATGG TCAGACCCGG TCTGATAAAA AAGGTCTGGT

11551 GTAGACAAGG CCTGCAGACC GTAAACCTGA GCCAGGCTTT CAAAAACTTG
CATCTGTTCC GGACGTCTGG CATTTGGACT CGGTCCGAAA GTTTTGAAC

11601 CAGGGGCTGT GGGGGGTGCG GGCTCCCACA GGCACCCGCG CGACCGTGTC
GTCCCCGACA CCCCCACGC CCGAGGGTGT CCGCTGGCGC GCTGGCACAG

11651 TAGCTTGCTG ACGCCCAACT CGCGCCTGTT GCTGCTGCTA ATAGCGCCCT
ATCGAACGAC TCGGGGTGA GCGCGGACAA CGACGACGAT TATCGCGGGA

11701 TCACGGACAG TGGCAGCGTG TCCCGGGACA CATACTAGG TCACTTGCTG
AGTGCTGTC ACCGTCGCAC AGGGCCCTGT GTATGGATCC AGTGAACGAC

11751 AACTGTACC GCGAGGCCAT AGGTCAGGCG CATGTGGACG AGCATACTTT
TGTGACATGG CGTCCGGTA TCCAGTCCGC GTACACCTGC TCGTATGAAA

11801 CCAGGAGATT ACAAGTGTC ACGCGCGCT GGGGCAGGAG GACACGGGCA
GGTCTCTAA GTTCACAGT CCGCGCGCA CCCCCTCCTC CTGTGCCCCG

11851 GCCTGGAGGC AACCCTAAC TACCTGCTGA CCAACCGGCG GCAGAAGATC
CGGACCTCCG TTGGGATTG ATGGACGACT GGTGGCCGC CGTCTTCTAG

11901 CCCTCGTTGC ACAGTTTAAA CAGCGAGGAG GAGCGCATTT TGCGCTACGT
GGGAGCAACG GTCAAATTT GTCGCTCCTC CTCGCGTAAA ACGCGATGCA

11951 GCAGCAGAGC GTGAGCCTTA ACCTGATGCG CGACGGGGTA ACGCCAGCG
CGTCGTCTCG CACTCGGAAT TGGACTACGC GCTGCCCAT TCGGGTTCG

12001 TGGCGCTGGA CATGACCGCG CGCAACATGG AACCAGGCAT GTATGCCTCA
ACCGCGACCT GTACTGGCGC GCGTTGTACC TTGGCCCGTA CATACGGAGT

12051 AACCAGCCGT TTATCAACCG CCAATGGAC TACTTGATC GCGCGGCCG
TTGGCCGGCA AATAGTTGGC GGATTACCTG ATGAACGTAG CGCGCCGGC

12101 CGTGAACCCC GAGTATTTCA CCAATGCCAT CTTGAACCCG CACTGGCTAC
GCACTTGGGG CTCATAAAGT GGTACGGTA GAACTTGGGC GTGACCGATG

12151 CGCCCCCTGG TTTCTACACC GGGGGATTG AGGTGCCCCA GGGTAACGAT
GCGGGGAC AAAGATGTGG CCCCCTAAGC TCCACGGGT CCCATTGCTA

12201 GGATTCCTCT GGGACGACAT AGACGACAGC GTGTTTCCC CGCAACCGCA
CCTAAGGAGA CCCTGCTGTA TCTGCTGTC CACAAAAGGG GCGTTGGCGT

Figure 27 M

12301 AGGAAAGCTT CCGCAGGCCA AGCAGCTTGT CCGATCTAGG CGCTGCGGCC
 TCCTTTCGAA GCGTCCGGT TCGTCGAACA GGCTAGATCC GCGACGCCGG

12351 CCGCGGTCAG ATGCTAGTAG CCCATTCCA AGCTTGATAG GGTCTCTTAC
 GCGCCAGTC TACGATCATC GGTAAAGGT TCGAATATC CCAGAGAATG

12401 CAGCACTCGC ACCACCCGCC CGCGCCTGCT GGGCGAGGAG GAGTACCTAA
 GTCGTGAGCG TGGTGGGCGG GCGCGGACGA CCCGCTCCTC CTCATGGATT

12451 ACAACTCGCT GCTGCAGCCG CAGCGCGAAA AAAACCTGCC TCCGGCATT
 TGTGAGCGA CGACGTCGGC GTCGCGCTTT TTTGGACGG AGGCCGTAAA

12501 CCCAACAAACG GGATAGAGAG CCTAGTGGAC AAGATGAGTA GATGGAAGAC
 GGGTTGTTGC CCTATCTCTC GGATCACCTG TTCTACTCAT CTACCTTCTG

12551 GTACGCGCAG GAGCACAGGG ACGTGCCAGG CCCGCGCCCG CCCACCCGTC
 CATGCGCGTC CTCGTGTCCC TGCACGGTCC GGGCGCGGGC GGGTGGGACG

12601 GTCAAAGGCA CGACCGTCAG CGGGGTCTGG TGTGGGAGGA CGATGACTCG
 CAGTTTCCGT GCTGGCAGTC GCGCCAGACC ACACCTCCT GCTACTGAGC

12651 GCAGACGACA GCAGCGTCCT GGATTTGGGA GGGAGTGGCA ACCCGTTTGC
 CGTCTGCTGT CGTCGCAGGA CCTAAACCCT CCCTCACCCT TGGGCAAACG

12701 GCACCTTCGC CCCAGGCTGG GGAGAATGTT TTAAAAAAA AAAAAGCATG
 CGTGGAAGCG GGGTCCGACC CCTCTTACAA AATTTTTTTT TTTTTCGTAC

12751 ATGCAAAATA AAAAATCAC CAAGGCCATG GCACCGAGCG TTGGTTTTCT
 TACGTTTTAT TTTTGTAGTG GTCCGGTAC CGTGGCTCGC AACCAAAAGA

12801 TGTATTCCCC TTAGTATGCG GCGCGCGGCG ATGTATGAGG AAGGTCCTCC
 ACATAAGGGG AATCATACGC GCGCGCGCGC TACATACTCC TTCCAGGAGG

12851 TCCCTCCTAC GAGAGTGTGG TGAGCGCGGC GCCAGTGGCG GCGGCGCTGG
 AGGGAGGATG CTCTCACACC ACTCGCGCCG CGGTCACCGC CGCCGCGACC

12901 GTTCTCCCTT CGATGCTCCC CTGGACCCGC CGTTTGTGCC TCCGCGGTAC
 CAAGAGGGAA GCTACGAGGG GACCTGGGCG GCAAACACGG AGGCGCCATG

12951 CTGCGGCCCTA CCGGGGGGAG AAACAGCATC CGTTACTCTG AGTTGGCACC
 GACGCCGGAT GGCCCCCTC TTTGTCGTAG GCAATGAGAC TCAACCGTGG

13001 CCTATTCGAC ACCACCCGTG TGTACCTGGT GGACAACAAG TCAACGGATG
 GGATAAGCTG TGGTGGGCAC ACATGGACCA CCTGTTGTTC AGTTGCCTAC

13051 TGGCATCCCT GAACTACCAG AACGACCACA GCAACTTTCT GACCACGGTC
 ACCGTAGGGA CTTGATGGTC TTGCTGGTGT CGTTGAAAGA CTGGTGCCAG

13101 ATTCAAAACA ATGACTACAG CCCGGGGGAG GCAAGCACAC AGACCATCAA
 TAAGTTTTGT TACTGATGTC GGGCCCCCTC CGTTCGTGTG TCTGGTAGTT

13151 TCTTGACGAC CGGTCGCACT GGGGCGGCGA CCTGAAAACC ATCCTGCATA
 AGAACTGCTG GCCAGCGTGA CCCCGCCGCT GGACTTTTGG TAGGACGTAT

Figure 27N

13251 CGGGTGATGG TGTCGCGCTT GCCTACTAAG GACAATCAGG TGGAGCTGAA
GCCCCACTACC ACAGCGCGAA CGGATGATTC CTGTTAGTCC ACCTCGACTT

13301 ATACGAGTGG GTGGAGTTCA CGCTGCCCCG GGGCAACTAC TCCGAGACCA
TATGCTCACC CACCTCAAGT GCGACGGGCT CCCGTTGATG AGGCTCTGGT

13351 TGACCATAGA CCTTATGAAC AACGCGATCG TGGAGCACTA CTTGAAAGTG
ACTGGTATCT GGAATACTTG TTGCGCTAGC ACCTCGTGAT GAACTTTCAC

13401 GGCAGACAGA ACGGGGTTCT GGAAGCGAC ATCGGGGTAA AGTTTGACAC
CCGTCTGTCT TGCCCAAGA CCTTTCGCTG TAGCCCCATT TCAAACGTG

13451 CCGCAACTTC AGACTGGGGT TTGACCCCGT CACTGGTCTT GTCATGCCTG
GGCGTTGAAG TCTGACCCCA AACTGGGGCA GTGACCAGAA CAGTACGGAC

13501 GGGTATATAC AAACGAAGCC TTCCATCCAG ACATCATTTT GCTGCCAGGA
CCCATATATG TTTGCTTCGG AAGGTAGGTC TGTAATAAAA CGACGGTCCT

13551 TGCGGGGTGG ACTTCACCCA CAGCCGCGCT AGCAACTTGT TGGGCATCCG
ACGCCCCACC TGAAGTGGGT GTCGGCGGAC TCGTTGAACA ACCCGTAGGC

13601 CAAGCGGCAA CCCTTCCAGG AGGGCTTTAG GATCACCTAC GATGATCTGG
GTTTCGCCGT GGGAAAGTCC TCCCGAAATC CTAGTGGATG CTACTAGACC

13651 AGGGTGGTAA CATTCCCGCA CTGTTGGATG TGGACGCCTA CCAGGCGAGC
TCCCACCATT GTAAGGGCGT GACAACCTAC ACCTGCGGAT GGTCCGCTCG

13701 TTGAAAGATG ACACCGAACA GGGCGGGGGT GGCGCAGGCG GCAGCAACAG
AACTTTCTAC TGTGGCTTGT CCCGCCCCCA CCGCGTCCGC CGTCGTTGTC

13751 CAGTGGCAGC GCGCGGAAG AGAACTCAA CGCGGCAGCC GCGGCAATGC
GTCAECGTCC CCGCGCCTTC TCTTGAGGTT GCGCCGTCGG CGCCGTACG

13801 AGCCGGTGGA GGACATGAAC GATCATGCCA TTCGCGGCGA CACCTTTGCC
TCGGCCACCT CCTGTACTTG CTAGTACGGT AAGCGCCGCT GTGGAAACGG

13851 ACACGGGCTG AGGAGAAGCG CGCTGAGGCC GAAGCAGCGG CCGAAGCTGC
TGTGCCCCGAC TCCTCTTCGC GCGACTCCGG CTTCGTCGCC GGCTTCGACG

13901 CGCCCCCGCT GCGCAACCCG AGGTCGAGAA GCCTCAGAAG AAACCGGTGA
GCGGGGGCGA CGCGTTGGGC TCCAGCTCTT CGGAGTCTTC TTTGGCCACT

13951 TCAAACCCCT GACAGAGGAC AGCAAGAAAC GCAGTTACAA CCTAATAAGC
AGTTTGGGGA CTGTCTCCTG TCGTCTTTG CGTCAATGTT GGATTATTCG

14001 AATGACAGCA CCTTCACCCA GTACCGCAGC TGGTACCTTG CATACTACTA
TTACTGTCGT GGAAGTGGGT CATGGCGTCG ACCATGGAAC GTATGTTGAT

14051 CGGCGACCCT CAGACCGGAA TCCGCTCATG GACCCTGCTT TGCACCTCTG
GCCGCTGGGA GTCTGGCCTT AGGCGAGTAC CTGGGACGAA ACGTGAGGAC

14101 ACGTAACCTG CGGCTCGGAG CAGGTCTACT GGTCGTTGCC AGACATGATG
TGCATTGGAC GCCGAGCCTC GTCCAGATGA CCAGCAACGG TCTGTACTAC

Figure 270

14201 GGTGGGCGCC GAGCTGTTGC CCGTGCACTC CAAGAGCTTC TACAACGACC
CCACCCGCGG CTCGACAACG GGCACGTGAG GTTCTCGAAG ATGTTGCTGG

14251 AGGCCGTCTA CTCCCAACTC ATCCGCCAGT TTACCTCTCT GACCCACGTG
TCCGGCAGAT GAGGGTTGAG TAGGCGGTCA AATGGAGAGA CTGGGTGCAC

14301 TTCAATCGCT TTCCCGAGAA CCAGATTTTG GCGCGCCCGC CAGCCCCAC
AAGTTAGCGA AAGGGCTCTT GGTCTAAAC CGCGCGGGCG GTCGGGGTG

14351 CATCACCACC GTCAGTGAAA ACGTTCCTGC TCTCACAGAT CACGGGACGC
GTAGTGGTGG CAGTCACTTT TGCAAGGACG AGAGTGCTA GTGCCCTGCG

14401 TACCGCTGCG CAACAGCATC GGAGGAGTCC AGCGAGTGAC CATTACTGAC
ATGGCGACGC GTTGTCTGAG CCTCCTCAGG TCGTCACTG GTAATGACTG

14451 GCCAGACGCC GCACCTGCCC CTACGTTTAC AAGGCCCTGG GCATAGTCTC
CGGTCTGCGG CGTGGACGGG GATGCAAATG TTCCGGGACC CGTATCAGAG

14501 GCCGCGCGTC CTATCGAGCC GCACTTTTTG AGCAAGCATG TCCATCCTTA
CGGCGCGCAG GATAGCTCGG CGTGAAAAAC TCGTTCGTAC AGGTAGGAAT

14551 TATCGCCCAG CAATAACACA GGCTGGGGCC TGCGCTTCCC AAGCAAGATG
ATAGCGGGTC GTTATTGTGT CCGACCCCGG ACGCGAAGGG TTCGTTCTAC

14601 TTTGGCGGGG CCAAGAAGCG CTCCGACCAA CACCCAGTGC GCGTGCGCGG
AAACCGCCCC GGTCTTCGC GAGGCTGGTT GTGGGTCACG CGCACGCGCC

14651 GCACTACCGC GCGCCCTGGG GCGCGCACAA ACGCGGCCGC ACTGGGCGCA
CGTGATGGCG CGCGGGACCC CGCGCGTGT TCGCGCGGCG TGACCCGCGT

14701 CCACCGTCGA TGACGCCATC GACGCGGTGG TGGAGGAGGC GCGCAACTAC
GGTGGCAGCT ACTGCGGTAG CTGCGCCACC ACCTCCTCCG CGCGTTGATG

14751 ACGCCACGC CGCCACCAGT GTCCACAGTG GACGCGGCCA TTCAGACCGT
TGCGGGTGCG GCGGTGGTCA CAGGTGTAC CTGCGCCGGT AAGTCTGGCA

14801 GGTGCGCGGA GCCCGGCGCT ATGCTAAAAT GAAGAGACGG CGGAGGCGCG
CCACGCGCCT CGGGCCGCGA TACGATTTTA CTTCTCTGCC GCCTCCGCGC

14851 TAGCACGTCG CCACCGCCGC CGACCCGGCA CTGCCGCCCA ACGCGCGGCG
ATCGTGACG GGTGGCGGCG GCTGGGCCGT GACGGCGGGT TGCGCGCCGC

14901 GCGGCCCTGC TTAACCGCGC ACGTCGCACC GGCCGACGGG CGGCCATGCG
CGCCGGGACG AATTGGCGCG TGCAGCGTGG CCGGCTGCCC GCCGGTACGC

14951 GGCCGCTCGA AGGCTGGCCG CGGGTATTGT CACTGTGCCC CCCAGGTCCA
CCGGCGAGCT TCCGACCGGC GCCATAACA GTGACACGGG GGGTCCAGGT

15001 GGCGACGAGC GGCCGCCGCA GCAGCCGCGG CCATTAGTGC TATGACTCAG
CCGCTGCTCG CCGCGGGCGT CGTCGGCGCC GGTAAATCAG ATACTGAGTC

15051 GGTGCGAGGG GCAACGTGTA TTGGGTGCGC GACTCGGTTA GCGGCCTGCG
CCAGCGTCCC CGTTGCACAT AACCACGCG CTGAGCCAAT CGCCGGACGC

Figure 27P

15151 ACTTAGACTC GTACTGTTGT ATGTATCCAG CGGCGGCGGC GCGCAACGAA
TGAATCTGAG CATGACAACA TACATAGGTC GCCGCCGCCG CGCGTTGCTT

15201 GCTATGTCCA AGCGCAAAAT CAAAGAAGAG ATGCTCCAGG TCATCGCGCC
CGATACAGGT TCGCGTTTTA GTTCTTCTC TACGAGGTCC AGTAGCGCGG

15251 GGAGATCTAT GGCCCCCGA AGAAGGAAGA GCAGGATTAC AAGCCCCGAA
CCTCTAGATA CCGGGGGGCT TCTTCCTTCT CGTCCTAATG TTCGGGGGCTT

15301 AGCTAAAGCG GGTCAAAAAG AAAAGAAAG ATGATGATGA TGAACCTGAC
TCGATTTCGC CCAGTTTTTC TTTTCTTTC TACTACTACT ACTTGAACCT

15351 GACGAGGTGG AACTGCTGCA CGCTACCGCG CCCAGGCGAC GGGTACAGTG
CTGCTCCACC TTGACGACGT GCGATGGCGC GGGTCCGCTG CCCATGTCAC

15401 GAAAGGTCTGA CGCGTAAAC GTGTTTTCG ACCCGGCACC ACCGTAGTCT
CTTTCAGCT GCGCATTTTG CACAAAACGC TGGGCCGTGG TGGCATCAGA

15451 TTACGCCCCG TGAGCGCTCC ACCCGCACCT ACAAGCGCGT GTATGATGAG
AATCGGGGCC ACTCGCGAGG TGGGCGTGA TGTTCGCGCA CATACTACTC

15501 GTGTACGGCG ACGAGGACCT GCTTGAGCAG GCCAACGAGC GCCTCGGGGA
CACATGCCGC TGCTCCTGGA CGAACTCGTC CGGTGCTCG CGGAGCCCCCT

15551 GTTGCCTAC GGAAAGCGGC ATAAGGACAT GCTGGCGTTG CCGCTGGACG
CAAACGGATG CCTTTCGCCG TATTCTGTA CGACCGCAAC GGCGACCTGC

15601 AGGGCAACCC AACACCTAGC CTAAAGCCCG TAACACTGCA GCAGGTGCTG
TCCCCTTGGG TTGTGGATCG GATTTCGGGC ATTGTGACGT CGTCCACGAC

15651 CCCGCGCTTG CACCGTCCGA AGAAAAGCGC GGCCTAAAGC GCGAGTCTGG
GGGCGCGAAC GTGGCAGGCT TCTTTTCGCG CCGGATTTCG CGCTCAGACC

15701 TGACTTGCCA CCCACCGTGC AGCTGATGGT ACCCAAGCGC CAGCGACTGG
ACTGAACCGT GGGTGGCACG TCGACTACCA TGGGTTTCGCG GTCGCTGACC

15751 AAGATGTCTT GGAAAAATG ACCGTGGAAC CTGGGCTGGA GCCCAGGTC
TTCTACAGAA CCTTTTTCAC TGGCACCTTG GACCCGACCT CGGGCTCCAG

15801 CGCGTGCGGC CAATCAAGCA GGTGGCGCCG GGAAGTGGCG TGCAGACCGT
GCGCACGCCG GTTAGTTTCGT CCACCGCGGC CCTGACCCGC ACGTCTGGCA

15851 GGACGTTTCAG ATACCCACTA CCAGTAGCAC CAGTATTGCC ACCGCCACAG
CCTGCAAGTC TATGGGTGAT GGTATCGTG GTCATAACGG TGGCGGTGTC

15901 AGGGCATGGA GACACAAACG TCCCCGGTTG CCTCAGCGGT GCGGGATGCC
TCCCGTACCT CTGTGTTTGC AGGGGCCAAC GGAGTCGCCA CCGCCTACGG

15951 GCGGTGCAGG CGGTCGCTGC GGCCGCGTCC AAGACCTCTA CGGAGGTGCA
CGCCACGTCC GCCAGCGACG CCGGCGCAGG TTCTGGAGAT GCCTCCACGT

16001 AACGGACCCG TGGATGTTTC GCGTTTCAGC CCCCCGGCGC CCGCGCCGTT
TTGCCTGGGC ACCTACAAAG CGCAAAGTCG GGGGGCCGCG GGCGCGGCAA

Figure 27A

16051 CGAGGAAGTA CGGCGCCGCC AGCGCGCTAC TGCCCGAATA TGCCCTACAT
GCTCCTTCAT GCCGCGGCGG TCGCGCGATG ACGGGCTTAT ACGGGATGTA

16101 CCTTCCATTG CGCCTACCCC CGGCTATCGT GGCTACACCT ACCGCCCCAG
GGAAGGTAAC GCGGATGGGG GCCGATAGCA CCGATGTGGA TGGCGGGGTC

16151 AAGACGAGCA ACTACCCGAC GCCGAACCAC CACTGGAACC CGCCGCCGCC
TTCTGCTCGT TGATGGGCTG CGGCTTGGTG GTGACCTTGG GCGGCGGCGG

16201 GTCGCCGTCG CCAGCCCGTG CTGGCCCCGA TTTCCGTGCG CAGGGTGGCT
CAGCGGCAGC GGTCGGGCAC GACCGGGGCT AAAGGCACGC GTCCACCCGA

16251 CGCGAAGGAG GCAGGACCCT GGTGCTGCCA ACAGCGCGCT ACCACCCAG
GCGCTTCCTC CGTCCTGGGA CCACGACGGT TGTCGCGCGA TGGTGGGGTC

16301 CATCGTTTAA AAGCCGGTCT TTGTGGTTCT TGCAGATATG GCCCTCACCT
GTAGCAAATT TTCGCCAGA AACACCAAGA ACCTCTATAC CGGGAGTGGa

16351 GCCGCCTCCG TTTCCCGGTG CCGGGATTCC GAGGAAGAAT GCACCGTAGG
CGGCGGAGGC AAAGGGCCAC GGCCCTAAGG CTCCTTCTTA CGTGGCATCC

16401 AGGGGCATGG CCGGCCACGG CCTGACGGGC GGCATGCGTC GTGCGCACCA
TCCCCGTACC GGCCGGTGCC GGACTGCCCC CCGTACGCAG CACGCGTGGT

16451 CCGGCGGCGG CGCGCGTCGC ACCGTGCGAT GCGCGGCGGT ATCCTGCCCC
GGCCGCCGCC GCGCGCAGCG TGGCAGCGTA GCGCGCGCCA TAGGACGGGG

16501 TCCTTATTCC ACTGATCGCC GCGGCGATTG GCGCCGTGCC CGGAATTGCA
AGGAATAAGG TGA CTAGCGG CGCCGCTAAC GCGGGCACGG GCCTTAACGT

16551 TCCGTGGCCT TGCAGGCGCA GAGACACTGA TTA AAAACAA GTTGCATGTG
AGGCACCGGA ACGTCCGCGT CTCTGTGACT AATTTTGTG CAACGTACAC

16601 GAAAAATCAA AATAAAAAGT CTGGACTCTC ACGCTCGCTT GGTCTGTAA
CTTTT TAGTT TTATTTTCA GACCTGAGAG TGCGAGCGAA CCAGGACATT

16651 CTATTTTGTG GAATGGAAGA CATCAACTTT GCGTCTCTGG CCCC GCGACA
GATAAAACAT CTTACCTTCT GTAGTTGAAA CGCAGAGACC GGGGCGCTGT

16701 CGGCTCGCGC CCGTTCATGG GAAACTGGCA AGATATCGGC ACCAGCAATA
GCCGAGCGCG GGCAAGTACC CTTTGACCGT TCTATAGCCG TGGTCGTTAT

16751 TGAGCGGTGG CGCCTTCAGC TGGGGCTCGC TGTGGAGCGG CATTAAAAAT
ACTCGCCACC GCGGAAGTCG ACCCCGAGCG ACACCTCGCC GTAATTTTAA

16801 TTCGGTTCCA CCGTTAAGAA CTATGGCAGC AAGGCCTGGA ACAGCAGCAC
AAGCCAAGGT GGCAATTCTT GATACCGTCG TTCCGGACCT TGTCGTCGTG

16851 AGGCCAGATG CTGAGGGATA AGTTGAAAGA GCAAAATTTC CAACAAAAGG
TCCGGTCTAC GACTCCCTAT TCAACTTTCT CGTTTTAAAG GTTGTTTCC

16901 TGGTAGATGG CCTGGCCTCT GGCATTAGCG GGGTGGTGGa CCTGGCCAAAC
ACCATCTACC GGACCGGAGA CCGTAATCGC CCCACCACCT GGACCGGTTG

16951 CAGGCAGTGC AAAATAAGAT TAACAGTAAG CTTGATCCCC GCCCTCCCGT
GTCCGTCACG TTTTATTCTA ATTGTCATTC GAACTAGGGG CGGGAGGGCA

Figure 27R

17051 AAAAGCGTCC GCGCCCCGAC AGGGAAGAAA CTCTGGTGAC GCAAATAGAC
TTTTCGCAGG CGCGGGGCTG TCCCTTCTTT GAGACCACTG CGTTTATCTG

17101 GAGCCTCCCT CGTACGAGGA GGCATAAAG CAAGGCCTGC CCACCACCCG
CTCGGAGGGA GCATGCTCCT CCGTGATTTC GTTCCGGACG GGTGGTGGG

17151 TCCCATCGCG CCCATGGCTA CCGGAGTGCT GGGCCAGCAC ACACCCGTAA
AGGGTAGCGC GGGTACCGAT GGCTCAGCA CCCGGTCGTG TGTGGGCATT

17201 CGCTGGACCT GCCTCCCCC GCCGACACCC AGCAGAAACC TGTGCTGCCA
GCGACCTGGA CGGAGGGGGG CGGCTGTGGG TCGTCTTTGG ACACGACGGT

17251 GGCCCCACCG CCGTTGTGTG AACCCGTCTT AGCCGCGCGT CCCTGCGCCG
CCGGGCTGGC GGCAACAACA TTGGGCAGGA TCGGCGCGCA GGGACGCGG

17301 CGCCGCCAGC GGTCCGCGAT CGTTGCGGCC CGTAGCCAGT GGCAACTGGC
CGCGCGGTG CAGGCGCTA GCAACGCCG GCATCGGTCA CCGTTGACCG

17351 AAAGCACACT GAACAGCATC GTGGGTCTGG GGGTGCAATC CCTGAAGCGC
TTTCGTGTGA CTTGTCTAG CACCCAGACC CCCACGTTAG GGAATTGCGC

17401 CGACGATGCT TCTGATAGCT AACGTGTCGT ATGTGTGTCA TGTATGCGTC
GCTGCTACGA AGACTATCGA TTGCACAGCA TACACACAGT ACATACGCAG

17451 CATGTCGCCG CCAGAGGAGC TGCTGAGCCG CCGCGCGCCC GCTTTCCAAG
GTACAGCGGC GGTCTCCTCG ACGACTCGGC GCGCGCGGG CGAAAGGTT

17501 ATGGGTACCC CTTGATGAT GCCGAGTGG TCTTACATGC ACATCTCGGG
TACCGATGGG GAAGCTACTA CGGCGTCACC AGAATGTACG TGTAGAGCCC

17551 CCAGGACGCC TCGGAGTACC TGAGCCCCG GCTGGTGACG TTTGCCCGG
GGTCTGCGG AGCCTCATGG ACTCGGGGCC CGACCACGTC AAACGGGCGC

17601 CCACCGAGAC GTACTTCAGC CTGAATAACA AGTTTAGAAA CCCCACGGT
GGTGGCTCTG CATGAAGTCG GACTTATTGT TCAAATCTTT GGGGTGCCAC

17651 GCGCCTACGC ACGACGTGAC CACAGACCGG TCCCAGCGTT TGACGCTGCG
CGCGGATGCG TGCTGCACTG GTGTCTGGCC AGGGTCGCAA ACTGCGACGC

17701 GTTCATCCCT GTGGACCGTG AGGATACTGC GTACTCGTAC AAGGCGCGGT
CAAGTAGGGA CACCTGGCAC TCCTATGACG CATGAGCATG TTCCGCGCCA

17751 TCACCCTAGC TGTGGGTGAT AACCGTGTGC TGGACATGGC TTCCACGTAC
AGTGGGATCG ACACCCACTA TTGGCACACG ACCTGTACCG AAGGTGCATG

17801 TTTGACATCC GCGGCGTGCT GGACAGGGGC CCTACTTTTA AGCCCTACTC
AAACTGTAGG CGCCGCACGA CCTGTCCCCG GGATGAAAAT TCGGGATGAG

17851 TGGCACTGCC TACAACGCCC TGGCTCCCAA GGGTGCCCCA AATCCTTGCG
ACCGTGACGG ATGTTGCGGG ACCGAGGGTT CCCACGGGGT TTAGGAACGC

17901 AATGGGATGA AGCTGCTACT GCTCTTGAAT TAAACCTAGA AGAAGAGGAC
TTACCCTACT TCGACGATGA CGAGAACTTT ATTTGGATCT TCTTCTCCTG

Figure 275


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17951 GATGACAACG AAGACGAAGT AGACGAGCAA GCTGAGCAGC AAAAAACTCA
      CTACTGTTGC TTCTGCTTCA TCTGCTCGTT CGACTCGTCG TTTTTTGAGT

18001 CGTATTTGGG CAGGCGCCTT ATTCTGGTAT AAATATTACA AAGGAGGGTA
      GCATAAACCC GTCCGCGGAA TAAGACCATA TTTATAATGT TTCCTCCCAT

18051 TTCAAATAGG TGTCGAAGGT CAAACACCTA AATATGCCGA TAAAACATTT
      AAGTTTATCC ACAGCTTCCA GTTTGTGGAT TTATACGGCT ATTTTGTAAA

18101 CAACCTGAAC CTCAAATAGG AGAATCTCAG TGGTACGAAA CAGAAATTAA
      GTTGGACTTG GAGTTTATCC TCTTAGAGTC ACCATGCTTT GTCTTTAATT

18151 TCATGCAGCT GGGAGAGTCC TAAAAAAGAC TACCCCAATG AAACCATGTT
      AGTACGTCGA CCTCTCAGG ATTTTCTCTG ATGGGGTTAC TTTGGTACAA

18201 ACGGTTTATA TGCAAAACCC ACAAATGAAA ATGGAGGGCA AGGCATTCTT
      TGCCAAGTAT ACGTTTTGGG TGTTTACTTT TACCTCCCGT TCCGTAAGAA

18251 GTAAAGCAAC AAAATGGAAA GCTAGAAAGT CAAGTGGAAA TGCAATTTTT
      CATTTCTGTTG TTTTACCTTT CGATCTTTCA GTTCACCTTT ACGTTAAAAA

18301 CTCAACTACT GAGGCAGCCG CAGGCAATGG TGATAACTTG ACTCCTAAAG
      GAGTTGATGA CTCCGTCGGC GTCCGTTACC ACTATTGAAC TGAGGATTTC

18351 TGGTATTGTA CAGTGAAGAT GTAGATATAG AAACCCAGAG CACTCATATT
      ACCATAACAT GTCACCTCTA CATCTATATC TTTGGGGTCT GTGAGTATAA

18401 TCTTACATGC CCACTATTAA GGAAGGTAAC TCACGAGAAC TAATGGGCCA
      AGAATGTACG GGTGATAATT CCTTCCATTG AGTGCTCTTG ATTACCCGGT

18451 ACAATCTATG CCCAACAGGC CTAATTACAT TGCTTTTAGG GACAATTTTA
      TGTTAGATAC GGGTTGTCCG GATTAATGTA ACGAAAATCC CTGTTAAAAA

18501 TTGGTCTAAT GTATTACAAC AGCACGGGTA ATATGGGTGT TCTGGCGGGC
      AACCAGATTA CATAATGTTG TCGTGCCCAT TATACCCACA AGACCGCCCG

18551 CAAGCATCGC AGTTGAATGC TGTTGTAGAT TTGCAAGACA GAAACACAGA
      GTTCGTAGCG TCAACTTACG ACAACATCTA AACGTTCTGT CTTTGTGTCT

18601 GCTTTCATAC CAGCTTTTGC TTGATTCCAT TGGTGATAGA ACCAGGTACT
      CGAAAGTATG GTCGAAAACG AACTAAGGTA ACCACTATCT TGGTCCATGA

18651 TTTCTATGTG GAATCAGGCT GTTGACAGCT ATGATCCAGA TGTTAGAATT
      AAAGATACAC CTTAGTCCGA CAACTGTCGA TACTAGGTCT ACAATCTTAA

18701 ATTGAAAATC ATGGAACCTG AGATGAACTT CCAAATTACT GCTTTCCACT
      TAACTTTTAG TACCTTGAAT TCTACTTGAA GGTTTAATGA CGAAAGGTGA

18751 GGGAGGTGTG ATTAATACAG AGACTCTTAC CAAGGTAAAA CCTAAAACAG
      CCTCCACAC TAATTATGTC TCTGAGAAATG GTTCCATTTT GGATTTTGTC

18801 GTCAGGAAAA TGGATGGGAA AAAGATGCTA CAGAATTTTC AGATAAAAAAT
      CAGTCCTTTT ACCTACCTTT TTTCTACGAT GTCTTAAAAG TCTATTTTAA

18851 GAAATAAGAG TTGGAAATAA TTTTGCCATG GAAATCAATC TAAATGCCAA
      CTTTATTCTC AACCTTTATT AAAACGGTAC CTTTAGTTAG ATTTACGGTT

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Figure 27T

18951 AGCTAAAGTA CAGTCCTTCC AACGTAAAAA TTTCTGATAA CCCAAACACC
TCGATTTCAT GTCAGGAAGG TTGCATTTTT AAAGACTATT GGGTTTGTGG

19001 TACGACTACA TGAACAAGCG AGTGGTGGCT CCCGGGCTAG TGGACTGCTA
ATGCTGATGT ACTTGTTCGC TCACCACCGA GGGCCCGATC ACCTGACGAT

19051 CATTAACTTT GGAGCACGCT GGTCCCTTGA CTATATGGAC AACGTCAACC
GTAATTGGAA CCTCGTGCGA CCAGGGAACT GATATACCTG TTGCAGTTGG

19101 CATTTAACCA CCACCGCAAT GCTGGCCTGC GCTACCGCTC AATGTTGCTG
GTAAATTGGT GGTGGCGTTA CGACCGGACG CGATGGCGAG TTACAACGAC

19151 GGCAATGGTC GCTATGTGCC CTTCCACATC CAGGTGCCTC AGAAGTTCTT
CCGTTACCAG CGATACACGG GAAGGTGTAG GTCCACGGAG TCTTCAAGAA

19201 TGCCATTAAA AACCTCCTTC TCCTGCCGGG CTCATACACC TACGAGTGGA
ACGGTAATTT TTGGAGGAAG AGGACGGCCC GAGTATGTGG ATGCTCACCT

19251 ACTTCAGGAA GGATGTAAAC ATGGTTCTGC AGAGCTCCCT AGGAAATGAC
TGAAGTCCTT CCTACAATTG TACCAAGACG TCTCGAGGGA TCCTTTACTG

19301 CTAAGGGTTG ACGGAGCCAG CATTAAGTTT GATAGCATTT GCCTTTACGC
GATTCCCAAC TGCCTCGGTC GTAATTCAA CTATCGTAAA CGGAAATGCG

19351 CACCTTCTTC CCCATGGCCC ACAACACCGC CTCCACGCTT GAGGCCATGC
GTGGAAGAAG GGGTACCGGG TGTTGTGGCG GAGGTGCGAA CTCCGGTACG

19401 TTAGAAACGA CACCAACGAC CAGTCCTTTA ACGACTATCT CTCCGCCGCC
AATCTTTGCT GTGGTTGCTG GTCAGGAAAT TGCTGATAGA GAGGCGGCGG

19451 AACATGCTCT ACCCTATACC CGCCAACGCT ACCAACGTGC CCATATCCAT
TTGTACGAGA TGGGATATGG GCGGTTGCGA TGGTTGCACG GGTATAGGTA

19501 CCCCTCCCGC AACTGGGCGG CTTTCCGCGG CTGGGCCTTC ACGCGCCTTA
GGGGAGGGCG TTGACCCGCC GAAAGGCGCC GACCCGGAAG TGCGCGGAAT

19551 AGACTAAGGA AACCCTATCA CTGGGCTCGG GCTACGACCC TTATTACACC
TCTGATTCCT TTGGGGTAGT GACCCGAGCC CGATGCTGGG AATAATGTGG

19601 TACTCTGGCT CTATACCCTA CCTAGATGGA ACCTTTTACC TCAACCACAC
ATGAGACCGA GATATGGGAT GGATCTACCT TGGAAAATGG AGTTGGTGTG

19651 CTTTAAGAAG GTGGCCATTA CCTTGACTC TTCTGTCAGC TGGCCTGGCA
GAAATTCCTC CACCGGTAAT GGAAACTGAG AAGACAGTCG ACCGGACCGT

19701 ATGACCGCCT GCTTACCCCC AACGAGTTTG AAATTAAGCG CTCAGTTGAC
TACTGGCGGA CGAATGGGGG TTGCTCAAAC TTAAATTCGC GAGTCAACTG

19751 GGGGAGGGTT ACAACGTTGC CCAGTGTAAC ATGACCAAAG ACTGGTTCCT
CCCCCCTCAA TGTTGCAACG GGTACATTG TACTGGTTTC TGACCAAGGA

19801 GGTACAAATG CTAGCTAACT ATAACATTGG CTACCAGGGC TTCTATATCC
CCATGTTTAC GATCGATTGA TATTGTAACC GATGGTCCCG AAGATATAGG

Figure 274

19851 CAGAGAGCTA CAAGGACCGC ATGTACTCCT TCTTTAGAAA CTTCCAGCCC
GTCTCTCGAT GTTCCTGGCG TACATGAGGA AGAAATCTTT GAAGGTCGGG

19901 ATGAGCCGTC AGGTGGTGGG TGATACTAAA TACAAGGACT ACCAACAGGT
TACTCGGCAG TCCACCACCT ACTATGATTT ATGTTCTCTGA TGGTTGTCCA

19951 GGGCATCCTA CACCAACACA ACAACTCTGG ATTTGTTGGC TACCTTGCCC
CCCGTAGGAT GTGGTTGTGT TGTGAGACC TAAACAACCG ATGGAACGGG

20001 CCACCATGCG CGAAGGACAG GCCTACCCTG CTAACCTCCC CTATCCGCTT
GGTGGTACGC GCTTCCTGTC CGGATGGGAC GATTGAAGGG GATAGGCGAA

20051 ATAGGCAAGA CCGCAGTTGA CAGCATTACC CAGAAAAAGT TTCTTTGCGA
TATCCGTTCT GCGGTCAACT GTCGTAATGG GTCTTTTCA AAGAAACGCT

20101 TCGCACCCCTT TGGCGCATCC CATTCTCCAG TAACTTTATG TCCATGGGCG
AGCGTGGGAA ACCGCGTAGG GTAAGAGGTC ATTGAAATAC AGGTACCCGC

20151 CACTCACAGA CCTGGGCCAA AACCTTCTCT ACGCCAACTC CGCCCACGCG
GTGAGTGTCT GGACCCGGTT TTGGAAGAGA TCGGTTGAG GCGGGTGGCG

20201 CTAGACATGA CTTTTGAGGT GGATCCCATG GACGAGCCCA CCCTTCTTTA
GATCTGTACT GAAAACCTCA CCTAGGGTAC CTGCTCGGGT GGGGAAGAAAT

20251 TGTTTTGTTT GAAGTCTTTG ACGTGGTCCG TGTGCACCAG CCGCACCGCG
ACAAAACAAA CTTCAGAAAC TGCACCAGGC ACACGTGGTC GCGGTGGCGC

20301 GCGTCATCGA AACCGTGTAC CTGCGCACGC CCTTCTCGGC CGGCAACGCC
CGCAGTAGCT TTGGCACATG GACGCGTGCG GGAAGAGCCG GCCGTTGGCG

20351 ACAACATAAA GAAGCAAGCA ACATCAACAA CAGCTGCCGC CATGGGCTCC
TGTTGTATTT CTCGTTTCGT TGTAGTTGTT GTCGACGGCG GTACCCGAGG

20401 AGTGAGCAGG AACTGAAAGC CATTGTCAA GATCTTGGTT GTGGGCCATA
TCACTCGTCC TTGACTTTCG GTAACAGTTT CTAGAACCAA CACCCGGTAT

20451 TTTTTTGGGC ACCTATGACA AGCGCTTTCC AGGCTTTGTT TCTCCACACA
AAAAAACCCG TGGATACTGT TCGCGAAAGG TCCGAAACAA AGAGGTGTGT

20501 AGCTCGCCTG CGCCATAGTC AATACGGCCG GTCGCGAGAC TGGGGGCGTA
TCGAGCGGAC GCGGTATCAG TTATGCCGGC CAGCGCTCTG ACCCCCGCAT

20551 CACTGGATGG CCTTGCCTG GAACCCGCAC TCAAAAACAT GCTACCTCTT
GTGACCTACC GGAAACGGAC CTTGGGCGTG AGTTTTGTA CGATGGAGAA

20601 TGAGCCCTTT GGCTTTTCTG ACCAGCGACT CAAGCAGGTT TACCAGTTG
ACTCGGAAA CCGAAAAGAC TGGTCGCTGA GTTCGTCAA ATGGTCAAAC

20651 AGTACGAGTC ACTCCTGCGC CGTAGCGCCA TTGCTTCTTC CCCCAGCCGC
TCATGCTCAG TGAGGACGCG GCATCGCGGT AACGAAGAAG GGGGCTGGCG

20701 TGTATAACGC TGGAAAAGTC CACCCAAAGC GTACAGGGGC CCAACTCGGC
ACATATTGCG ACCTTTTCAG GTGGGTTTCG CATGTCCCCG GGTTGAGCCG

20751 CGCCTGTGGA CTATTCTGCT GCATGTTTCT CCACGCCTTT GCCAACTGGC
GCGGACACCT GATAAGACGA CGTACAAAGA GGTGCGGAAA CGGTTGACCG

Figure 27 V.

20851 CCCAACTCCA TGCTCAACAG TCCCCAGGTA CAGCCCACCC TCGCTCGCAA
 GGGTTGAGGT ACGAGTTGTC AGGGGTCCAT GTCGGGTGGG ACGCAGCGTT
 20901 CCAGGAACAG CTCTACAGCT TCCTGGAGCG CCACTCGCCC TACTTCCGCA
 GGTCTTTGTC GAGATGTCGA AGGACCTCGC GGTGAGCGGG ATGAAGGCGT
 20951 GCCACAGTGC GCAGATTAGG AGCGCCACTT CTTTTTGTCA CTGAAAAAC
 CGGTGTCACG CGTCTAATCC TCGCGGTGAA GAAAAACAGT GAACTTTTTG
 21001 ATGTAAAAAT AATGTACTAG AGACACTTTC AATAAAGGCA AATGCTTTTA
 TACATTTTTA TTACATGATC TCTGTGAAAG TTATTTCCGT TTACGAAAAAT
 21051 TTTGTACACT CTCGGGTGAT TATTTACCCC CACCCTTGCC GTCTGCGCCG
 AAACATGTGA GAGCCCACTA ATAAATGGGG GTGGGAACGG CAGACGCGG
 21101 TTTAAAAATC AAAGGGGTTC TGCCGCGCAT CGCTATGCGC CACTGGCAGG
 AAATTTTTAG TTTCCCAAG ACGGCGCGTA GCGATACGCG GTGACCGTCC
 21151 GACACGTTGC GATACTGGTG TTAGTGCTC CACTTAACT CAGGCACAAC
 CTGTGCAACG CTATGACCAC AAATCAGAG GTGAATTGA GTCCGTGTTG
 21201 CATCCGCGGC AGCTCGGTGA AGTTTTCACT CCACAGGCTG CGCACCATCA
 GTAGGCGCCG TCGAGCCACT TCAAAAAGTGA GGTGTCCGAC GCGTGGTAGT
 21251 CCAACGCGTT TAGCAGGTCG GGCGCCGATA TCTTGAAGTC GCAGTTGGGG
 GGTGCGCAA ATCGTCCAGC CCGCGGTAT AGAACTTCAG CGTCAACCCC
 21301 CCTCCGCCCT GCGCGCGCGA GTTGCATAC ACAGGGTTC AGCACTGGAA
 GGAGGCGGGA CGCGCGCGCT CAACGCTATG TGTCCCAACG TCGTGACCTT
 21351 CACTATCAGC GCCGGGTGGT GCACGCTGGC CAGCACGCTC TTGTGCGAGA
 GTGATAGTCG CGGCCACCA CGTGCGACCG GTCGTGCGAG AACAGCCTCT
 21401 TCAGATCCGC GTCCAGGTCC TCCGCGTTGC TCAGGGCGAA CGGAGTCAAC
 AGTCTAGGCG CAGGTCCAGG AGGCGCAACG AGTCCCGCTT GCCTCAGTTG
 21451 TTTGGTAGCT GCCTTCCCAA AAAGGGCGCG TGCCAGGCT TTGAGTTGCA
 AAACCATCGA CGGAAGGTT TTTCCGCGC ACGGGTCCGA AACTCAACGT
 21501 CTCGCACCGT AGTGGCATCA AAAGGTGACC GTGCCCCGTC TGGGCGTTAG
 GAGCGTGGCA TCACCGTAGT TTTCCACTGG CACGGGCCAG ACCCGCAATC
 21551 GATACAGCGC CTGCATAAAA GCCTTGATCT GCTTAAAAGC CACCTGAGCC
 CTATGTCGCG GACGTATTTT CGGAAGTAGA CGAATTTTCG GTGGACTCGG
 21601 TTTGCGCCTT CAGAGAAGAA CATGCCGCAA GACTTGCCGG AAAACTGATT
 AAACCGGAA GTCTCTTCTT GTACGGCGTT CTGAACGGCC TTTTGACTAA
 21651 GGCCGGACAG GCCGCGTCGT GCACGCAGCA CCTTGCGTCG GTGTTGGAGA
 CCGGCCTGTC CGGCGCAGCA CGTGCGTCGT GGAACGCAGC CACAACCTCT
 21701 TCTGCACCAC ATTTCCGGCC CACCGGTTCT TCACGATCTT GGCCTTGCTA
 AGACGTGGTG TAAAGCCGGG GTGGCCAAGA AGTGCTAGAA CCGGAACGAT

Figure 27 W

21801 AATCACGTGC TCCTTATTTA TCATAATGCT TCCGTGTAGA CACTTAAGCT
 TTAGTGACAG AGGAATAAAT AGTATTACGA AGGCACATCT GTGAATTCGA
 21851 CGCCTTCGAT CTCAGCGCAG CGGTGCAGCC ACAACGCGCA GCCCGTGGGC
 GCGGAAGCTA GAGTCGCGTC GCCACGTCCG TGTTCGCGCT CGGGCACCCG
 21901 TCGTGATGCT TGTAGGTCAC CTCTGCAAAC GACTGCAGGT ACGCCTGCAG
 AGCACTACGA ACATCCAGTG GAGACGTTTG CTGACGTCCA TCGGACGTC
 21951 GAATCGCCCC ATCATCGTCA CAAAGGTCTT GTTGCTGGTG AAGGTCAGCT
 CTTAGCGGGG TAGTAGCAGT GTTTCAGAA CAACGACCAC TTCCAGTCGA
 22001 GCAACCCGCG GTGCTCCTCG TTCAGCCAGG TCTTGCCATAC GGCCGCCAGA
 CGTTGGGCGC CACGAGGAGC AAGTCGGTCC AGAACGTATG CCGGCGGTCT
 22051 GCTTCCACTT GGTCAAGCAG TAGTTTGAAG TTCGCCTTTA GATCGTTATC
 CGAAGGTGAA CCAGTCCGTC ATCAAACCTC AAGCGGAAAT CTAGCAATAG
 22101 CACGTGGTAC TTGTCCATCA GCGCGCGCGC AGCCTCCATG CCCTTCTCCC
 GTGCACCATG AACAGGTAGT CGCGCGCGCG TCGGAGGTAC GGGGAAGAGG
 22151 ACGCAGACAC GATCGGCACA CTCAGCGGGT TCATCACCGT AATTTCACTT
 TGCGTCTGTG CTAGCCGTGT GAGTCGCCCC AGTAGTGGCA TTAAAGTGAA
 22201 TCCGCTTCGC TGGGCTCTTC CTCTTCCTCT TCGCTCCGCA TACCACGCGC
 AGGCGAAGCG ACCCGAGAAG GAGAAGGAGA ACGCAGGCGT ATGGTGCGCG
 22251 CACTGGGTCTG TCTTCATTCA GCCGCCGCAC TGTGCGCTTA CCTCCTTTGC
 GTGACCCAGC AGAAGTAAGT CGGCGGCGTG ACACGCGAAT GGAGGAAACG
 22301 CATGCTTGAT TAGCACCGGT GGGTTGCTGA AACCACCAT TTGTAGCGCC
 GTACGAACCTA ATCGTGGCCA CCCAACGACT TTGGGTGGTA AACATCGCGG
 22351 ACATCTTCTC TTTCTTCCTC GCTGTCCACG ATTACCTCTG GTGATGGCGG
 TGTAAGAGAG AAAGAAGGAG CGACAGGTGC TAATGGAGAC CACTACCGCC
 22401 GCGCTCGGGC TTGGGAGAAG GGCGCTTCTT TTTCTTCTTG GGCGCAATGG
 CGCGAGCCCG AACCTCTTC CCGCGAAGAA AAAGAAGAAC CCGCGTTACC
 22451 CCAAATCCGC CGCCGAGGTC GATGGCCGCG GGCTGGGTGT GCGCGGCACC
 GGTTTAGGCG GCGGCTCCAG CTACCGGCGC CCGACCCACA CGCGCCGTGG
 22501 AGCGCGTCTT GTGATGAGTC TTCCTCGTCC TCGGACTCGA TACGCCGCCT
 TCGCGCAGAA CACTACTCAG AAGGAGCAGG AGCCTGAGCT ATGCGGCGGA
 22551 CATCCGCTTT TTTGGGGGCG CCCGGGGAGG CGGCGGCGAC GGGGACGGGG
 GTAGGCGAAA AAACCCCGC GGGCCCTCC GCGCGCGTG CCCCTGCCCC
 22601 ACGACACGTC CTCCATGGTT GGGGGACGTC GCGCCGCACC GCGTCCGCGC
 TGCTGTGCAG GAGGTACCAA CCCCCTGCAG CGCGGCGTGG CGCAGGCGCG
 22651 TCGGGGGTGG TTTGCGGCTG CTCCTCTTCC CGACTGGCCA TTTCTTCTC
 AGCCCCCACC AAAGCGCGAC GAGGAGAAGG GCTGACCGGT AAAGGAAGAG

Figure 27 X

22751 CCGCCCCCTC TGAGTTCGCC ACCACCGCCT CCACCGATGC CGCCAACGCG
GGCGGGGGAG ACTCAAGCGG TGGTGGCGGA GGTGGCTACG GCGGTTGCGC

22801 CCTACCACCT TCCCCGTCGA GGCACCCCG CTTGAGGAGG AGGAAAGTGAT
GGATGGTGGA AGGGGCAGCT CCGTGGGGGC GAACTCCTCC TCCTTCACTA

22851 TATCGAGCAG GACCCAGGTT TTGTAAGCGA AGACGACGAG GACCGCTCAG
ATAGCTCGTC CTGGGTCCAA AACATTGCT TCTGCTGCTC CTGGCGAGTC

22901 TACCAACAGA GGATAAAAAG CAAGACCAGG ACAACGCAGA GGCAAACGAG
ATGGTTGTCT CCTATTTTTC GTTCTGGTCC TGTTCGCTCT CCGTTTGCTC

22951 GAACAAGTCG GCGGGGGGA CGAAAGGCAT GCGGACTACC TAGATGTGGG
CTTGTTACAG CCGCCCCCT GCTTTCGTA CCGCTGATGG ATCTACACCC

23001 AGACGACGTG CTGTTGAAGC ATCTGCAGCG CCAGTGCGCC ATTATCTGCG
TCTGCTGCAC GACAACTTCG TAGACGTCGC GGTACGCGG TAATAGACGC

23051 ACGCGTTGCA AGAGCGCAGC GATGTGCCCC TCGCCATAGC GGATGTCAGC
TGCGCAACGT TCTCGCGTCG CTACACGGGG AGCGGTATCG CCTACAGTCG

23101 CTTGCCTACG AACGCCACCT ATTCTCACC GCGTACCCC CCAAACGCCA
GAACGGATGC TTGCGGTGGA TAAGAGTGGC GCGCATGGGG GGTTCGCGT

23151 AGAAAACGGC ACATGCGAGC CCAACCCGCG CCTCAACTTC TACCCCGTAT
TCTTTTGCCG TGTACGCTCG GGTGCGCGC GGAGTTGAAG ATGGGGCATA

23201 TTGCCGTGCC AGAGGTGCTT GCCACCTATC ACATCTTTT CCAAACTGC
AACGGCACGG TCTCCACGAA CCGTGGATAG TGTAGAAAAA GGTTTGACG

23251 AAGATACCCC TATCTGCGG TGCCAACCGC AGCCGAGCGG ACAAGCAGCT
TTCTATGGGG ATAGGACGGC ACGGTTGGCG TCGGCTCGCC TGTTGTCGA

23301 GGCCTTGCGG CAGGGCGCTG TCATACCTGA TATCGCCTCG CTCAACGAAG
CCGGAACGCC GTCCCGCGAC AGTATGGACT ATAGCGGAGC GAGTTGCTTC

23351 TGCCAAAAAT CTTTGAGGGT CTTGGACGCG ACGAGAAGCG CGCGGCAAAC
ACGGTTTTTA GAAACTCCCA GAACCTGCGC TGCTCTTCGC GCGCCGTTTG

23401 GCTCTGCAAC AGGAAAACAG CGAAAATGAA AGTCACTCTG GAGTGTGGT
CGAGACGTTG TCCTTTTGTC GCTTTTACTT TCAGTGAGAC CTCACAACCA

23451 GGAATCGAG GGTGACAACG CGCGCCTAGC CGTACTAAAA CGCAGCATCG
CCTTGAGCTC CCACTGTTGC GCGCGGATCG GCATGATTTT GCGTCGTAGC

23501 AGGTCACCCA CTTTGCCCTAC CCGGCACTTA ACCTACCCCC CAAGGTCATG
TCCAGTGGGT GAAACGGATG GGCCGTGAAT TGGATGGGGG GTTCCAGTAC

23551 AGCACAGTCA TGAGTGAGCT GATCGTGCGC CGTGCGCAGC CCCTGGAGAG
TCGTGTCAGT ACTCACTCGA CTAGCACGCG GCACGCGTCG GGGACCTCTC

23601 GGATGCAAAT TTGCAAGAAC AAACAGAGGA GGGCCTACCC GCAGTTGGCG
CCTACGTTTA AACGTTCTTG TTTGTCTCCT CCCGGATGGG CGTCAACCGC

Figure 27 Y

23701 GAGCGACGCA AACTAATGAT GGCCGCAGTG CTCGTTACCG TGGAGCTTGA
CTCGCTGCGT TTGATTACTA CCGGCGTCAC GAGCAATGGC ACCTCGAACT

23751 GTGCATGCAG CGGTTCTTTG CTGACCCGGA GATGCAGCGC AAGCTAGAGG
CACGTACGTC GCCAAGAAAC GACTGGGCCT CTACGTCGCG TTCGATCTCC

23801 AAACATTGCA CTACACCTTT CGACAGGGCT ACGTACGCCA GGCCTGCAAG
TTTGTAACGT GATGTGGAAA GCTGTCCCGA TGCATGCGGT CCGGACGTTT

23851 ATCTCCAACG TGGAGCTCTG CAACCTGGTC TCCTACCTTG GAATTTTGCA
TAGAGGTTGC ACCTCGAGAC GTTGGACCAG AGGATGGAAC CTTAAAACGT

23901 CGAAAACCGC CTTGGGCAAA ACGTGCTTCA TTCCACGCTC AAGGGCGAGG
GCTTTTGGCG GAACCCGTTT TGCACGAAGT AAGGTGCGAG TTCCCGCTCC

23951 CGCGCCGCGA CTACGTCCGC GACTGCGTTT ACTTATTTCT ATGCTACACC
GCGCGGCGCT GATGCAGGCG CTGACGCAAA TGAATAAAGA TACGATGTGG

24001 TGGCAGACGG CCATGGGCGT TTGGCAGCAG TGCTTGGAGG AGTGCAACCT
ACCGTCTGCC GGTACCCGCA AACCCTCGTC ACGAACCTCC TCACGTTGGA

24051 CAAGGAGCTG CAGAAACTGC TAAAGCAAAA CTTGAAGGAC CTATGGACGG
GTTCTCGAC GTCTTTGACG ATTTCTGTTT GAACTTCCTG GATACCTGCC

24101 CCTTCAACGA GCGCTCCGTG GCCGCGCACC TGGCGGACAT CATTTTCCCC
GGAAGTTGCT CGCGAGGCAC CGGCGCGTGG ACCGCCTGTA GTAAAAGGGG

24151 GAACGCCTGC TTAATAACCTT GCAACAGGGT CTGCCAGACT TCACCAGTCA
CTTGCGGACG AATTTTGGGA CGTTGTCCCA GACGGTCTGA AGTGGTCAGT

24201 AAGCATGTTG CAGAACTTTA GGAACCTTAT CCTAGAGCGC TCAGGAATCT
TTCGTACAAC GTCTTGAAAT CCTTGAAATA GGATCTCGCG AGTCCTTAGA

24251 TGCCCGCCAC CTGCTGTGCA CTTCTAGCG ACTTTGTGCC CATTAGTAC
ACGGGCGGTG GACGACACGT GAAGGATCGC TGAAACACGG GTAATTCATG

24301 CGCGAATGCC CTCGCGCGCT TTGGGGCCAC TGCTACCTTC TGCAGCTAGC
GCGCTTACGG GAGGCGGCGA AACCCCGGTG ACGATGGAAG ACGTCGATCG

24351 CAACTACCTT GCCTACCACT CTGACATAAT GGAAGACGTG AGCGGTGACG
GTTGATGGAA CGGATGGTGA GACTGTATTA CCTTCTGCAC TCGCCACTGC

24401 GTCTACTGGA GTGTCACTGT CGCTGCAACC TATGCACCCC GCACCGCTCC
CAGATGACCT CACAGTGACA GCGACGTTGG ATACGTGGGG CGTGGCGAGG

24451 CTGGTTTGCA ATTTCGAGCT GCTTAACGAA AGTCAAATTA TCGGTACCTT
GACCAAACGT TAAGCGTCGA CGAATTGCTT TCAGTTTAAT AGCCATGGAA

24501 TGAGCTGCAG GGTCCCTCGC CTGACGAAAA GTCCGCGGCT CCGGGGTTGA
ACTCGACGTC CCAGGGAGCG GACTGCTTTT CAGGCGCCGA GGCCCCAAT

24551 AACTCACTCC GGGGCTGTGG ACGTCGGCTT ACCTTCGCAA ATTTGTACCT
TTGAGTGAGG CCCCACACC TGCAGCCGAA TGGAAGCGTT TAAACATGGA

Figure 272

24601 GAGGACTACC ACGCCACGA GATTAGGTTT TACGAAGACC AATCCCGCCC
CTCCTGATGG TCGGGTGCT CTAATCCAAG ATGCTTCTGG TTAGGGCGGG

24651 GCCTAATGCG GAGCTTACCG CCTGCGTCAT TACCCAGGGC CACATTCTTG
CGGATTACGC CTCGAATGGC GGACGCAGTA ATGGGTCCCC GTGTAAGAAC

24701 GCCAATTGCA AGCCATCAAC AAAGCCCGCC AAGAGTTTCT GCTACGAAAG
CGGTAAACGT TCGGTAGTTG TTTCCGGCGG TTCTCAAAGA CGATGCTTTC

24751 GGACGGGGGG TTTACTTGGA CCCCCAGTCC GCGGAGGAGC TCAACCCAAT
CCTGCCCCC AAATGAACCT GGGGGTCAGG CCGCTCCTCG AGTTGGGTTA

24801 CCCCCGCGG CCGCAGCCCT ATCAGCAGCA GCCCGGGGCC CTTGCTTCCC
GGGGGCGGC GCGCTCGGA TAGTCGTCGT CCGCGCCCGG GAACGAAGGG

24851 AGGATGGCAC CAAAAAGAA GCTGCAGCTG CCGCCGCCAC CCACGGACGA
TCCTACCGTG GGTTTTCTT CGACGTCGAC GCGGCGGGTG GGTGCCTGCT

24901 GGAGGAATAC TGGGACAGTC AGGCAGAGGA GGTTTTGGAC GAGGAGGAGG
CCTCCTTATG ACCCTGTCAG TCCGTCTCCT CCAAACCTG CTCTCCTCC

24951 AGGACATGAT GGAAGACTGG GAGAGCCTAG ACGAGGAAGC TTCCGAGGTC
TCCTGTACTA CTTCTGACC CTCTCGGATC TGCTCCTTCG AAGGCTCCAG

25001 GAAGAGGTGT CAGACGAAAC ACCGTCACCC TCGGTGCGAT TCCCTCGCC
CTTCTCCACA GTCTGCTTTG TGGCAGTGGG AGCCAGCGTA AGGGGAGCGG

25051 GGCGCCCCAG AAATCGGCAA CCGGTTCAG CATGGCTACA ACCTCCGCTC
CCGCGGGGTC TTAGCCGTT GGCCAAGGTC GTACCGATGT TGGAGGCGAG

25101 CTCAGGCGCC GCCGGCACTG CCGGTTCGCC GACCCAACCG TAGATGGGAC
GAGTCCGCGG CCGCCGTGAC GGGCAAGCGG CTGGGTTGGC ATCTACCTG

25151 ACCACTGGAA CCAGGGCCGG TAAGTCCAAG CAGCCGCCGC CGTTAGCCCA
TGGTGACCTT GGTCCCGGCC ATTCAGGTTT GTCCGGCGCG GCAATCGGGT

25201 AGAGCAACAA CAGCGCCAAG GCTACCGCTC ATGGCGCGGG CACAAGAAGC
TCTCGTTGTT GTCGCGGTTT CGATGGCGAG TACCGCGCCC GTGTTCTTGC

25251 CCATAGTTGC TTGCTTGCAA GACTGTGGGG GCAACATCTC CTTGCCCCGC
GGTATCAACG AACGAACGTT CTGACACCCC CGTTGTAGAG GAAGCGGGCG

25301 CGCTTTCTTC TCTACCATCA CCGCGTGGCC TTCCCCGTA ACATCCTGCA
GCGAAAGAAG AGATGCTAGT GCCGCACCGG AAGGGGGCAT TGTAGGACGT

25351 TTTACTACCGT CATCTCTACA GCCCATACTG CACCGGCGGC AGCGGCAGCA
AATGATGGCA GTAGAGATGT CCGGTATGAC GTGGCCGCCG TCGCCGTCGT

25401 ACAGCAGCGG CCACACAGAA GCAAAGGCGA CCGGATAGCA AGACTCTGAC
TGTCGTCGCC GGTGTGTCTT CGTTTCCGCT GGCCTATCGT TCTGAGACTG

25451 AAAGCCCAAG AAATCCACAG CGGCGGCAGC AGCAGGAGGA GGAGCGCTGC
TTTCGGGTTC TTTAGGTGTC GCCGCCGTCG TCGTCTCCTT CCTCGCGACG

25501 GTCTGGCGCC CAACGAACCC GTATCGACCC GCGAGCTTAG AAACAGGATT
CAGACCGCGG GTTGCTTGGG CATAGCTGGG CGCTCGAATC TTTGTCTAA

Figure 27 AA

25551 TTTCCCACTC TGTATGCTAT ATTTCAACAG AGCAGGGGCC AAGAACAAGA
AAAGGGTGAG ACATACGATA TAAAGTTGTC TCGTCCCCGG TTCTTGTCT

25601 GCTGAAAATA AAAACAGGT CTCTGCGATC CCTCACCCGC AGCTGCCTGT
CGACTTTTAT TTTTGTCCA GAGACGCTAG GGAGTGGGCG TCGACGGACA

25651 ATCACAAAAG CGAAGATCAG CTTCGGCGCA CGCTGGAAGA CGCGGAGGCT
TAGTGTTTTT GCTTCTAGTC GAAGCCGCGT GCGACCTTCT GCGCCTCCGA

25701 CTCTTCAGTA AATACTGCGC GCTGACTCTT AAGGACTAGT TTCGCGCCCT
GAGAAGTCAT TTATGACGCG CGACTGAGAA TTCTGATCA AAGCGCGGGA

25751 TTCTCAAATT TAAGCGCGAA AACTACGTCA TCTCCAGCGG CCACACCCGG
AAGAGTTTAA ATTGCGGCTT TTGATGCAGT AGAGGTCGCC GGTGTGGGCG

25801 CGCCAGCACC TGTGTGCAGC GCCATTATGA GCAAGGAAAT TCCCACGCCC
CGGGTCGTGG ACAACAGTCG CGGTAATACT CGTTCCTTTA AGGGTGCGGG

25851 TACATGTGGA GTTACCAGCC ACAAATGGGA CTTGCGGCTG GAGCTGCCCCA
ATGTACACCT CAATGGTCGG TGTTTACCCT GAACGCCGAC CTCGACGGGT

25901 AGACTACTCA ACCCGAATAA ACTACATGAG CGCGGGACCC CACATGATAT
TCTGATGAGT TGGGCTTATT TGATGTACTC GCGCCTGGG GTGTACTATA

25951 CCCGGGTCAA CGGAATACGC GCCCACCAGG ACCGAATTCT CCTGGAACAG
GGGCCAGTT GCCTTATGCG CGGGTGCGTT TGGCTTAAGA GGACCTTGTC

26001 GCGGTATTA CCACCACACC TCGTAATAAC CTTAATCCCC GTAGTTGGCC
CGCCGATAAT GGTGGTGTGG AGCATTATG GAATTAGGGG CATCAACCGG

26051 CGCTGCCCTG GTGTACCAGG AAAGTCCCGC TCCCACCACT GTGGTACTTC
GCGACGGGAC CACATGGTCC TTTCAGGGCG AGGGTGGTGA CACCATGAAG

26101 CCAGAGACGC CCAGGCCGAA GTTCAGATGA CTAACTCAGG GGCGCAGCTT
GGTCTCTGCG GGTCCGGCTT CAAGTCTACT GATTGAGTCC CCGCGTCGAA

26151 GCGGGCGGCT TTCGTACAG GGTGCGGTCG CCCGGGCAGG GTATAACTCA
CGCCCGCCGA AAGCAGTGTC CCACGCCAGC GGGCCCGTCC CATATTGAGT

26201 CCTGACAATC AGAGGGCGAG GTATTTCAGCT CAACGACGAG TCGGTGAGCT
GGACTGTTAG TCTCCCGCTC CATAAGTCGA GTTGCTGCTC AGCCACTCGA

26251 CCTCGCTTGG TCTCCGTCCG GACGGGACAT TTCAGATCGG CGGCGCCGGC
GGAGCGAACC AGAGGCAGGC CTGCCCTGTA AAGTCTAGCC GCCGCGGCCG

26301 CGCTCTTCAT TCACGCCTCG TCAGGCAATC CTAACCTCTG AGACCTCGTC
GCGAGAAGTA AGTGCGGAGC AGTCCGTTAG GATTGAGACG TCTGGAGCAG

26351 CTCTGAGCCG CGCTCTGGAG GCATTGGAAC TCTGCAATTT ATTGAGGAGT
GAGACTCGGC GCGAGACCTC CGTAACCTTG AGACGTTAAA TAACTCCTCA

26401 TTGTGCCATC GGTCTACTTT AACCCTTCT CGGGACCTCC CGGCCACTAT
AACACGGTAG CCAGATGAAA TTGGGGAAGA GCCCTGGAGG GCCGGTGATA

26451 CCGGATCAAT TTATTCCTAA CTTTGACGCG GTAAAGGACT CGGCGGACGG
GGCCTAGTTA AATAAGGATT GAAACTGCGC CATTCCTGA GCCGCCTGCC

Figure 27 AB

26501 CTACGACTGA ATGTTAAGTG GAGAGGCAGA GCAACTGCGC CTGAAACACC
GATGCTGACT TACAATTACAC CTCTCCGTCT CGTTGACGCG GACTTTGTGG

26551 TGGTCCACTG TCGCCGCCAC AAGTGCTTTG CCCGCGACTC CGGTGAGTTT
ACCAGGTGAC AGCGGCGGTG TTCACGAAAC GGGCGCTGAG GCCACTCAAA

26601 TGCTACTTTG AATTGCCCCG GGATCATATC GAGGGCCCGG CGCACGGCGT
ACGATGAAAC TTAACGGGCT CCTAGTATAG CTCCC GGCC GCGTGCCGCA

26651 CCGGCTTACC GCCCAGGGAG AGCTTGCCCG TAGCCTGATT CGGGAGTTTA
GGCCGAATGG CGGGTCCCTC TCGAACGGGC ATCGGACTAA GCCCTCAAAT

26701 CCCAGCGCCC CCTGCTAGTT GAGCGGGACA GGGGACCCTG TGTTCCTACT
GGGTGCGGGG GGACGATCAA CTCGCCCTGT CCCCTGGGAC ACAAGAGTGA

26751 GTGATTTGCA ACTGTCTTAA CCCTGGATTA CATCAAGATC TTTGTTGCCA
CACTAAACGT TGACAGGATT GGGACCTAAT GTAGTTCTAG AAACAACGGT

26801 TCTCTGTGCT GAGTATAATA AATACAGAAA TTAAATATA CTGGGGCTCC
AGAGACACGA CTCATATTAT TTATGTCTTT AATTTTATAT GACCCCGAGG

26851 TATCGCCATC CTGTAAACGC CACCGTCTTC ACCCGCCCAA GCAAACCAAG
ATAGCGGTAG GACATTTGCG GTGGCAGAAG TGGGCGGGTT CGTTTGGTTC

26901 GCGAACCTTA CCTGGTACTT TTAACATCTC TCCCTCTGTG ATTTACAACA
CGCTTGGAAT GGACCATGAA AATTGTAGAG AGGGAGACAC TAAATGTTGT

26951 GTTTCAACCC AGACGGAGTG AGTCTACGAG AGAACCTCTC CGAGCTCAGC
CAAAGTTGGG TCTGCCTCAC TCAGATGCTC TCTTGAGAG GCTCGAGTCG

27001 TACTCCATCA GAAAAACAC CACCCTCCTT ACCTGCCGGG AACGTACGAG
ATGAGGTAGT CTTTTTTGTG GTGGGAGGAA TGGACGGCCC TTGCATGCTC

27051 TGCCTCACCG GCCGCTGCAC CACACCTACC GCCTGACCGT AAACCAGACT
ACGCAGTGGC CGGCGACGTG GTGTGGATGG CGGACTGGCA TTTGGTCTGA

27101 TTTTCCGGAC AGACCTCAAT AACTCTGTTT ACCAGAACAG GAGGTGAGCT
AAAAGGCCTG TCTGGAGTTA TTGAGACAAA TGGTCTTGTC CTCCACTCGA

27151 TAGAAAACCC TTAGGGTATT AGGCCAAAGG CGCAGCTACT GTGGGGTTTA
ATCTTTTGGG AATCCCATAA TCCGTTTCC GCGTCGATGA CACCCCAAAT

27201 TGAACAATTC AAGCAACTCT ACGGGCTATT CTAATTCAGG TTTCTCTAGA
ACTTGTTAAG TTCGTTGAGA TGCCCGATAA GATTAAGTCC AAAGAGATCT

27251 ATCGGGGTTG GGGTTATTCT CTGTCTTG TG ATTCTCTTTA TTCTTATACT
TAGCCCCAAC CCCAATAAGA GACAGAACAC TAAGAGAAAT AAGAATATGA

27301 AACGCTTCTC TGCCTAAGGC TCGCCGCCTG CTGTGTGCAC ATTTGCATTT
TTGCCAAGAG ACGGATTCCG AGCGGCGGAC GACACACGTG TAAACGTAAA

27351 ATTGTCAGCT TTTTAAACGC TGGGGTCGCC ACCCAAGATG ATTAGGTACA
TAACAGTCGA AAAATTTGCG ACCCCAGCGG TGGGTTCTAC TAATCCATGT

27401 TAATCCTAGG TTTACTCACC CTTGCGTCAG CCCACGGTAC CACCCAAAAG
ATTAGGATCC AAATGAGTGG GAACGCAGTC GGGTGCCATG GTGGGTTTTC

Figure 27AC

27451 GTGGATTTTA AGGAGCCAGC CTGTAATGTT ACATTGCGAG CTGAAGCTAA
CACCTAAAAT TCCTCGGTCG GACATTACAA TGTAAGCGTC GACTTCGATT

27501 TGAGTGCACC ACTCTTATAA AATGCACCAC AGAACATGAA AAGCTGCTTA
ACTCACGTGG TGAGAATATT TTACGTGGTG TCTTGACTT TTCGACGAAT

27551 TTCGCCACAA AAACAAAATT GGCAAGTATG CTGTTTATGC TATTTGGCAG
AAGCGGTGTT TTTGTTTTAA CCGTTCATAC GACAAATACG ATAAACCGTC

27601 CCAGGTGACA CTACAGAGTA TAATGTTACA GTTTTCCAGG GTAAAGTCA
GGTCCACTGT GATGTCTCAT ATTACAATGT CAAAAGGTCC CATTTTCAGT

27651 TAAAACTTTT ATGTATACTT TTCCATTTTA TGAAATGTGC GACATTACCA
ATTTTGAAAA TACATATGAA AAGGTAAAAT ACTTTACACG CTGTAATGTT

27701 TGTACATGAG CAAACAGTAT AAGTTGTGGC CCCCACAAAA TTGTGTGGAA
ACATGTACTC GTTTGTCATA TTCAACACCG GGGGTGTTTT AACACACCTT

27751 AACACTGGCA CTTTCTGCTG CACTGCTATG CTAATTACAG TGCTCGCTTT
TTGTGACCGT GAAAGACGAC GTGACGATAC GATTAATGTC ACGAGCGAAA

27801 GGTCTGTACC CTA CTCTATA TTAATACAA AAGCAGACGC AGCTTTATTG
CCAGACATGG GATGAGATAT AATTATGTT TTCGTCTGCG TCGAAATAAC

27851 AGGAAAAGAA AATGCCTTAA TTTACTAAGT TACAAAGCTA ATGTCACCAC
TCCTTTTCTT TTACGGAATT AAATGATTCA ATGTTTCGAT TACAGTGGTG

27901 TAACTGCTTT ACTCGCTGCT TGCAAAACAA ATTCAAAAAG TTAGCATTAT
ATTGACGAAA TGAGCGACGA ACGTTTGTGTT TAAGTTTTTC AATCGTAATA

27951 AATTAGAATA GGATTTAAAC CCCCCGGTCA TTTCTGCTC AATACCATTC
TTAATCTTAT CCTAAATTG GGGGGCCAGT AAAGGACGAG TTATGGTAAG

28001 CCCTGAACAA TTGACTCTAT GTGGGATATG CTCCAGCGCT ACAACCTTGA
GGGACTTGTT AACTGAGATA CACCCTATAC GAGGTGCGGA TGTTGGAAC

28051 AGTCAGGCTT CCTGGATGTC AGCATCTGAC TTTGGCCAGC ACCTGTCCCG
TCAGTCCGAA GGACCTACAG TCGTAGACTG AAACCGGTCG TGGACAGGGC

28101 CGGATTTGTT CCAGTCCAAC TACAGCGACC CACCCTAACA GAGATGACCA
GCCTAAACAA GGTCAGGTTG ATGTCGCTGG GTGGGATTGT CTCTACTGGT

28151 ACACAACCAA CGCGCCCGCC GCTACCGGAC TTACATCTAC CACAAATACA
TGTGTTGGTT GCGCCGGCGG CGATGGCCTG AATGTAGATG GTGTTTATGT

28201 CCCCAAGTTT CTGCCTTTGT CAATAACTGG GATAACTTGG GCATGTGGTG
GGGTTTCAAA GACGGAAACA GTTATTGACC CTATTGAACC CGTACACCAC

28251 GTTCTCCATA GCGCTTATGT TTGTATGCCT TATTATTATG TGGCTCATCT
CAAGAGGTAT CGCGAATACA AACATACGGA ATAATAATAC ACCGAGTAGA

28301 GCTGCCTAAA GCGCAAACGC GCGGACCAC CCATCTATAG TCCCATCATT
CGACGGATTT CGCGTTTGCG CGGGCTGGTG GGTAGATATC AGGGTAGTAA

28351 GTGCTACACC CAAACAATGA TGGAAATCCAT AGATTGGACG GACTGAAACA
CACGATGTGG GTTTGTACT ACCTTAGGTA TCTAACCTGC CTGACTTTGT

Figure 27A D

28451 TTTTATATTA CTGACCCCTG TTGCGCTTTT TTGTGCGTGC TCCACATTGG
AAAATATAAT GACTGGGAAC AACGCGAAAA AACACGCACG AGGTGTAACC

28501 CTGCGGTTTC TCACATCGAA GTAGACTGCA TTCCAGCCTT CACAGTCTAT
GACGCCAAAG AGTGTAGCTT CATCTGACGT AAGGTCGGAA GTGTCAGATA

28551 TTGCTTTACG GATTTGTAC C CTCACGCTC ATCTGCAGCC TCATCACTGT
AACGAAATGC CTAAACAGTG GGAGTCCGAG TAGACGTCGG AGTAGTGACA

28601 GGTCAATCGCC TTTATCCAGT GCATTGACTG GGTCTGTGTG CGCTTTGCAT
CCAGTAGCGG AAATAGGTCA CGTAACTGAC CCAGACACAC GCGAAACGTA

28651 ATCTCAGACA CCATCCCCAG TACAGGGACA GGACTATAGC TGAGCTTCTT
TAGAGTCTGT GGTAGGGGTC ATGTCCCTGT CCTGATATCG ACTCGAAGAA

28701 AGAATTTCTT AATTATGAAA TTTACTGTGA CTTTCTGTCT GATTATTTGC
TCTTAAGAAA TTAATACTTT AAATGACACT GAAAAGACGA CTAATAAACG

28751 ACCCTATCTG CGTTTTGTTC CCCGACCTCC AAGCCTCAAA GACATATATC
TGGGATAGAC GCAAAACAAG GGGCTGGAGG TTCGGAGTTT CTGTATATAG

28801 ATGCAGATTC ACTCGTATAT GGAATATTCC AAGTTGCTAC AATGAAAAAA
TACGTCTAAG TGAGCATATA CTTATAAGG TTCAACGATG TTACTTTTTT

28851 GCGATCTTTC CGAAGCCTGG TTATATGCAA TCATCTCTGT TATGGTGTTC
CGCTAGAAAG GCTTCGGACC AATATACGTT AGTAGAGACA ATACCACAAG

28901 TGCAGTACCA TCTTAGCCCT AGCTATATAT CCCTACCTTG ACATTGGCTG
ACGTCATGGT AGAATCGGGA TCGATATATA GGGATGGAAC TGTAAACGAC

28951 GAACGCAATA GATGCCATGA ACCACCCAAC TTTCCCGCG CCCGCTATGC
CTTGCGTTAT CTACGGTACT TGGTGGGTTG AAAGGGGCGC GGGCGATACG

29001 TTCCACTGCA ACAAGTTGTT GCCGGCGGCT TTGTCCCAGC CAATCAGCCT
AAGGTGACGT TGTTCACAAA CGGCCGCCGA AACAGGGTCG GTTAGTCGGA

29051 CGCCACCTT CTCCACCCC CACTGAAATC AGCTACTTTA ATCTAACAGG
GCGGGTGGA GAGGGTGGGG GTGACTTTAG TCGATGAAAT TAGATTGTCC

29101 AGGAGATGAC TGACACCCTA GATCTAGAAA TGGACGGAAT TATTACAGAG
TCCTCTACTG ACTGTGGGAT CTAGATCTTT ACCTGCCTTA ATAATGTCTC

29151 CAGCGCCTGC TAGAAAGACG CAGGGCAGCG GCCGAGCAAC AGCGCATGAA
GTCGCGGACG ATCTTTCTGC GTCCCGTCGC CGGCTCGTTG TCGCGTACTT

29201 TCAAGAGCTC CAAGACATGG TTAACCTGCA CCAAGTCAAA AGGGGTATCT
AGTTCTCGAG GTTCTGTACC AATTGAACGT GGTCACGTTT TCCCCATAGA

29251 TTTGTCTCGT AAAGCAGGCC AAAGTCACCT ACGACAGTAA TACCACCGGA
AAACAGAGCA TTTCGTCCGG TTTCAGTGGA TGCTGTCATT ATGGTGGCCT

29301 CACCGCCTTA GCTACAAGTT GCCAACCAAG CGTCAGAAAT TGGTGGTCAT
GTGGCGGAAT CGATGTTCAA CGGTTGGTTC GCAGTCTTTA ACCACCAGTA

Figure 27AE

29401 GCTGCATTCA CTCACCTTGT CAAGGACCTG AGGATCTCTG CACCCCTTATT
CGACGTAAGT GAGTGGAAACA GTTCCTGGAC TCCTAGAGAC GTGGGAATAA

29451 AAGACCCTGT GCGGTCTCAA AGATCTTATT CCCTTTAACT AATAAAAAAA
TTCTGGGACA CGCCAGAGTT TCTAGAATAA GGGAAATTGA TTATTTTTTT

29501 AATAATAAAG CATCACTTAC TTAAATCAG TTAGCAAATT TCTGTCCAGT
TTATTATTTC GTAGTGAATG AATTTTAGTC AATCGTTTAA AGACAGGTCA

29551 TTATTTCAGCA GCACCTCCTT GCCCTCCTCC CAGCTCTGGT ATTGCAGCTT
AATAAGTCGT CGTGGAGGAA CGGGAGGAGG GTCGAGACCA TAACGTCGAA

29601 CCTCCTGGCT GCAAACCTTC TCCACAATCT AAATGGAATG TCAGTTTCCT
GGAGGACCGA CGTTTGAAG AGGTGTTAGA TTTACCTTAC AGTCAAAGGA

29651 CCTGTTCTCTG TCCATCCGCA CCCACTATCT TCATGTTGTT GCAGATGAAG
GGACAAGGAC AGGTAGGCGT GGGTGATAGA AGTACAACAA CGTCTACTTC

29701 CGCGCAAGAC CGTCTGAAGA TACCTTCAAC CCCGTGTATC CATATGACAC
GCGCGTCTG GCAGACTTCT ATGGAAGTTG GGGCACATAG GTATACTGTG

29751 GGAACCCGGT CCTCCAACG TGCCTTTTCT TACTCCTCCC TTTGTATCCC
CCTTTGGCCA GGAGTTGAC ACGGAAAAGA ATGAGGAGGG AAACATAGGG

29801 CCAATGGGTT TCAAGAGAGT CCCCTGGGG TACTCTCTTT GCGCCTATCC
GGTTACCCAA AGTTCTCTCA GGGGGACCCC ATGAGAGAAA CGCGGATAGG

29851 GAACCTCTAG TTACCTCCAA TGGCATGCTT GCGCTCAAAA TGGGCAACGG
CTTGGAGATC AATGGAGGTT ACCGTACGAA CGCGAGTTT ACCCGTTGCC

29901 CCTCTCTCTG GACGAGGCCG GCAACCTTAC CTCCCAAAAT GTAACCACTG
GGAGAGAGAC CTGCTCCGGC CGTTGGAATG GAGGGTTTAA CATTGGTGAC

29951 TGAGCCCACC TCTCAAAAAA ACCAAGTCAA ACATAAACCT GGAAATATCT
ACTCGGGTGG AGAGTTTTTT TGGTTCAGTT TGTATTGGA CTTTATAGA

30001 GCACCCCTCA CAGTTACCTC AGAAGCCCTA ACTGTGGCTG CCGCCGACG
CGTGGGGAGT GTCAATGGAG TCTTCGGGAT TGACACCGAC GGCGGCGTGG

30051 TCTAATGGTC GCGGGCAACA CACTCACCAT GCAATCACAG GCCCCGCTAA
AGATTACCAG CGCCCGTTGT GTGAGTGGTA CGTTAGTGTC CGGGGCGATT

30101 CCGTGCACGA CTCCAACTT AGCATTGCCA CCCAAGGACC CCTCACAGTG
GGCACGTGCT GAGGTTTGAA TCGTAACGCT GGGTTCCTGG GGAGTGTAC

30151 TCAGAAGGAA AGCTAGCCCT GCAAACATCA GGCCCCCTCA CCACCACCGA
AGTCTTCCTT TCGATCGGGA CGTTTGTAGT CCGGGGGAGT GGTGGTGGCT

30201 TAGCAGTACC CTTACTATCA CTGCCTCACC CCCTCTAACT ACTGCCACTG
ATCGTCATGG GAATGATAGT GACGGAGTGG GGGAGATTGA TGACGGTGAC

30251 GTAGCTTGGG CATTGACTTG AAAGAGCCCA TTTATACACA AAATGGAAAA
CATCGAACCC GTAACGTAAC TTTCTCGGGT AAATATGTGT TTTACCTTTT

Figure 27 AF

30351 TTTGACCGTA GCAACTGGTC CAGGTGTGAC TATTAATAAT ACTTCCTTGC
 AAACCTGGCAT CGTTGACCAG GTCCACACTG ATAATTATTA TGAAGGAACG
 30401 AAACATAAGT TACTGGAGCC TTGGGTTTTG ATTCAACAAG CAATATGCAA
 TTTGATTTC AATGACCTCGG AACCCAAAAC TAAGTGTTC GTTATACGTT
 30451 CTTAATGTAG CAGGAGGACT AAGGATTGAT TCTCAAAACA GACGCCTTAT
 GAATTACATC GTCTCTCTGA TTCCTAATA AGAGTTTGT CTGCGGAATA
 30501 ACTTGATGTT AGTTATCCGT TTGATGCTCA AAACCAACTA AATCTAAGAC
 TGAACATCAA TCAATAGGCA AACTACGAGT TTTGGTTGAT TTAGATTCTG
 30551 TAGGACAGGG CCCTCTTTTT ATAACTCAG CCCACAACCT GGATATTAAC
 ATCCTGTCCC GGGAGAAAAA TATTTGAGTC GGGTGTGAA CCTATAATTG
 30601 TACAACAAAG GCCTTTACTT GTTACAGCT TCAACAATT CCAAAAAGCT
 ATGTTGTTTC CGGAAATGAA CAAATGTGCA AGTTTGTAA GGTTTTTCGA
 30651 TGAGGTAAAC CTAAGCACTG CCAAGGGGTT GATGTTTGAC GCTACAGCCA
 ACTCCAATTG GATTCTGTGAC GGTCCCCCAA CTACAACTG CGATGTCCGT
 30701 TAGCCATTAA TGCAGGAGAT GGGCTTGAAT TTGGTTCACC TAATGCACCA
 ATCGGTAATT ACGTCTCTA CCCGAACCTA AACCAAGTGG ATTACGTGGT
 30751 AACACAAATC CCCTCAAAAC AAAAATTGGC CATGGCCTAG AATTTGATTC
 TTGTGTTTAG GGGAGTTTG TTTTAAACCG GTACCGGATC TTAAACTAAG
 30801 AAACAAGGCT ATGGTTCCTA AACTAGGAAC TGGCCTTAGT TTTGACAGCA
 TTTGTTCCGA TACCAAGGAT TTGATCCTTG ACCGGAATCA AAACGTGCTG
 30851 CAGGTGCCAT TACAGTAGGA AACAAAAATA ATGATAAGCT AACTTTGTGG
 GTCCACGGTA ATGTCATCCT TTGTTTTAT TACTATTCGA TTGAAACACC
 30901 ACCACACCAG CTCCATCTCC TAACTGTAGA CTAAATGCAG AGAAAGATGC
 TGGTGTGGTC GAGGTAGAGG ATTGACATCT GATTACGTC TCTTCTACG
 30951 TAACTCACT TTGGTCTTAA CAAAATGTGG CAGTCAATA CTTGCTACAG
 ATTTGAGTGA AACCAGAAAT GTTTTACACC GTCAGTTTAT GAACGATGTC
 31001 TTTCAAGTTT GGCTGTTAAA GGCAGTTTGG CTCCAATATC TGGAACAGTT
 AAAGTCAAAA CCGACAATT CCGTCAAACC GAGGTTATAG ACCTTGTCOA
 31051 CAAAGTGCTC ATCTTATTAT AAGATTGAC GAAAATGGAG TGCTACTAAA
 GTTTCACGAG TAGAATAATA TTCTAACTG CTTTACCTC ACGATGATTT
 31101 CAATTCTTTC CTGGACCCAG AATATTGGA CTTTAGAAT GGAGATCTTA
 GTTAAGGAAG GACCTGGGTC TTATAACCTT GAAATCTTTA CCTCTAGAAT
 31151 CTGAAGGCAC AGCCTATACA AACGCTGTTG GATTATGCC TAACCTATCA
 GACTTCCGTG TCGGATATGT TTGCGACAAC CTAAATACGG ATTGGATAGT
 31201 GCTTATCCAA AATCTCACGG TAAACTGCC AAAAGTAACA TTGTCACTCA
 CGAATAGGTT TTAGAGTGCC ATTTGACGG TTTTCATTGT AACAGTCAGT

Figure 27 AG

31251 AGTTTACTTA AACGGAGACA AAACATAACC TGTAACACTA ACCATTACAC
TCAAATGAAT TTGCCTCTGT TTTGATTGG ACATTGTGAT TGGTAATGTG

31301 TAAACGGTAC ACAGGAAACA GGAGACACAA CTCCAAGTGC ATACTCTATG
ATTTGCCATG TGTCCTTTGT CCTCTGTGTT GAGGTTCACG TATGAGATAC

31351 TCATTTTCAT GGGACTGGTC TGGCCACAAC TACATTAATG AAATATTGTC
AGTAAAAGTA CCCTGACCAG ACCGGTGTG ATGTAATTAC TTTATAAACG

31401 CACATCCTCT TACACTTTT CATACTTGC CCAAGAATAA AGAATCGTTT
GTGTAGGAGA ATGTGAAAAA GTATGTAACG GGTCTTATT TCTTAGCAAA

31451 GTGTTATGTT TCAACGTGTT TATTTTCAA TTGCAGAAAA TTTCAAGTCA
CACAATACAA AGTTGCACAA ATAAAAAGTT AACGTCTTTT AAAGTTCAGT

31501 TTTTTCATTC AGTAGTATAG CCCACCACC ACATAGCTTA TACAGATCAC
AAAAAGTAAG TCATCATATC GGGGTGGTGG TGTATCGAAT ATGTCTAGTG

31551 CGTACCTTAA TCAAACTCAC AGAACCTAG TATTCAACCT GCCACCTCCC
GCATGGAATT AGTTTGAGTG TCTTGGGATC ATAAGTTGGA CGGTGGAGGG

31601 TCCCAACACA CAGAGTACAC AGTCCTTTCT CCCC GGCTGG CCTTAAAAAG
AGSGTTGTGT GTCTCATGTG TCAGGAAAGA GGGGCCGACC GGAATTTTTC

31651 CATCATATCA TGGGTAACAG ACATATTCTT AGGTGTTATA TTCCACACGG
GTAGTATAGT ACCCATGTG TGTATAAGAA TCCACAATAT AAGGTGTGCC

31701 TTTCTGTGCG AGCCAAACGC TCATCAGTGA TATTAATAAA CTCCCCGGGC
AAAGGACAGC TCGGTTTGCG AGTAGTCACT ATAATTATTT GAGGGGCCCC

31751 AGCTCACTTA AGTTCATGTC GCTGTCCAGC TGCTGAGCCA CAGGCTGCTG
TCGAGTGAAT TCAAGTACAG CGACAGGTCG ACGACTCGGT GTCCGACGAC

31801 TCCAACTTGC GGTGCTTAA CGGGCGGCGA AGGAGAAGTC CACGCCTACA
AGGTTGAACG CCAACGAATT GCCCGCCGCT TCCTCTTCAG GTGCGGATGT

31851 TGGGGGTAGA GTCATAATCG TGCATCAGGA TAGGGCGGTG GTGCTGCAGC
ACCCCCATCT CAGTATTAGC ACGTAGTCTT ATCCCGCCAC CACGACGTCG

31901 AGCGCGCGAA TAAACTGCTG CCGCGCGCGC TCCGTCCTGC AGGAATACAA
TCGCGCGCTT ATTTGACGAC GCGCGCGCGC AGGCAGGACG TCCTTATGTT

31951 CATGGCAGTG GTCTCCTCAG CGATGATTCG CACCGCCCGC AGCATAAGGC
GTACCGTCAC CAGAGGAGTC GCTACTAAGC GTGGCGGGCG TCGTATTCCG

32001 GCCTTGTCCT CCGGGCACAG CAGCGCACCC TGATCTCACT TAAATCAGCA
CGGAACAGGA GGCCCGTGTC GTCGCGTGGG ACTAGAGTGA ATTTAGTCGT

32051 CAGTAACTGC AGCACAGCAC CACAATATTG TTCAAAATCC CACAGTGCAA
GTCATTGACG TCGTGTCTGT GTGTTATAAC AAGTTTTAGG GTGTCACGTT

32101 GCGCTGTAT CCAAAGCTCA TGGCGGGGAC CACAGAACCC ACGTGCCAT
CCGCGACATA GGTTCGAGT ACCGCCCCTG GTGCTTGGG TGCACCGGTA

32151 CATACCACAA GCGCAGGTAG ATTAAGTGGC GACCCCTCAT AAACACGCTG
GTATGGTGTG CGCGTCCATC TAATTCACCG CTGGGGAGTA TTTGTGCGAC

Figure 27AH

32251 CCATATAAAC CTCTGATTAA ACATGGCGCC ATCCACCACC ATCCTAAACC
GGTATATTTG GAGACTAATT TGTACCGCGG TAGGTGGTGG TAGGATTTGG

32301 AGCTGGCCAA AACCTGCCCCG CCGGCTATAC ACTGCAGGGA ACCGGGACTG
TCGACCGGTT TTGGACGGGC GGCCGATATG TGACGTCCCT TGGCCCTGAC

32351 GAACAATGAC AGTGGAGAGC CCAGGACTCG TAACCATGGA TCATCATGCT
CTTGTTACTG TCACCTCTCG GGTCTGAGC ATTGGTACCT AGTAGTACGA

32401 CGTCATGATA TCAATGTTGG CACAACACAG GCACACGTGC ATACACTTCC
GCAGTACTAT AGTTACAACC GTGTGTGTGC CGTGTGCACG TATGTGAAGG

32451 TCAGGATTAC AAGCTCCTCC CGCGTTAGAA CCATATCCCA GGAACAACC
AGTCCTAATG TTCGAGGAGG GCGCAATCTT GGTATAGGGT CCCTTGTGG

32501 CATTCTGAA TCAGCGTAAA TCCCACACTG CAGGGAAGAC CTCGCACGTA
GTAAGGACTT AGTCGCATTT AGGGTGTGAC GTCCCTTCTG GAGCGTGCAT

32551 ACTCACGTTG TGCATTGTCA AAGTGTTACA TTCGGGCAGC AGCGGATGAT
TGAGTGCAAC ACGTAACAGT TTCACAATGT AAGCCCGTCG TCGCCTACTA

32601 CCTCCAGTAT GGTAGCGCGG GTTCTGTCT CAAAAGGAGG TAGACGATCC
GGAGGTCATA CCATCGCGCC CAAAGACAGA GTTTTCCTCC ATCTGCTAGG

32651 CTACTGTACG GAGTGCGCCG AGACAACCGA GATCGTGTG GTCGTAGTGT
GATGACATGC CTCACGCGGC TCTGTTGGCT CTAGCACAAC CAGCATCACA

32701 CATGCCAAAT GGAACGCCGG ACGTAGTCAT ATTTCTGAA GCAAAACCAG
GTACGGTTTA CCTTGCGGCC TGCATCAGTA TAAAGGACTT CGTTTGGTC

32751 GTGCGGGCGT GACAAACAGA TCTGCGTCTC CGGTCTCGCC GCTTAGATCG
CACGCCCCGA CTGTTTGTCT AGACGCAGAG GCCAGAGCGG CGAATCTAGC

32801 CTCTGTGTAG TAGTTGTAGT ATATCCACTC TCTCAAAGCA TCCAGGCGCC
GAGACACATC ATCAACATCA TATAGGTGAG AGAGTTTCGT AGGTCCGCGG

32851 CCCTGGCTTC GGGTTCTATG TAAACTCCTT CATGCGCCGC TGCCCTGATA
GGGACCGAAG CCAAGATAC ATTTGAGGAA GTACGCGGCG ACGGGACTAT

32901 ACATCCACCA CCGCAGAATA AGCCACACCC AGCCAACCTA CACATTCGTT
TGTAGGTGGT GCGCTCTTAT TCGGTGTGGG TCGGTTGGAT GTGTAAGCAA

32951 CTGCGAGTCA CACACGGGAG GAGCGGGAAG AGCTGGAAGA ACCATGTTTT
GACGCTCAGT GTGTGCCCTC CTCGCCCTTC TCGACCTTCT TGGTACAAAA

33001 TTTTTTTATT CCAAAGATT ATCCAAAACC TCAAAATGAA GATCTATTAA
AAAAAATAA GGTTTTCTAA TAGGTTTTGG AGTTTTACTT CTAGATAATT

33051 GTGAACGCGC TCCCCTCCGG TGGCGTGGTC AAACCTCTACA GCCAAAGAAC
CACTTGCGCG AGGGGAGGCC ACCGCACCAG TTTGAGATGT CGGTTTCTTG

33101 AGATAATGGC ATTTGTAAGA TGTGACAA TGGCTTCCAA AAGGCAAACG
TCTATTACCG TAAACATTCT ACAACGTGTT ACCGAAGGTT TTCCGTTTGC

Figure 27 AI

33201 CTCTATAAAC ATTCCAGCAC CTTCAACCAT GCCCAAATAA TTCTCATCTC
GAGATATTTG TAAGGTCGTG GAAGTTGGTA CGGGTTTATT AAGAGTAGAG

33251 GCCACCTTCT CAATATATCT CTAAGCAAAT CCCGAATATT AAGTCCGGCC
CGGTGGAAGA GTTATATAGA GATTCTTTA GGGCTTATAA TTCAGGCCGG

33301 ATTGTAAAAA TCTGCTCCAG AGCGCCCTCC ACCTTCAGCC TCAAGCAGCG
TAACATTTTT AGACGAGGTC TCGCGGGAGG TGGAAAGTCGG AGTTCGTGCG

33351 AATCATGATT GCAAAAATTC AGGTTCCTCA CAGACCTGTA TAAGATTCAA
TTAGTACTAA CGTTTTTAAG TCCAAGGAGT GTCTGGACAT ATTCTAAGTT

33401 AAGCGGAACA TTAACAAAAA TACCGCGATC CCGTAGGTCC CTTGCGAGGG
TTCGCCTTGT AATTGTTTTT ATGGCGCTAG GGCATCCAGG GAAGCGTCCC

33451 CCAGCTGAAC ATAATCGTGC AGGTCTGCAC GGACCAGCGC GGCCACTTCC
GGTCGACTTG TATTAGCACG TCCAGACGTG CCTGGTCGCG CCGGTGAAGG

33501 CCGCCAGGAA CCATGACAAA AGAACCACACA CTGATTATGA CACGCATACT
GGCGGTCTTT GGTACTGTTT TCTTGGGTGT GACTAATACT GTGCGTATGA

33551 CGGAGCTATG CTAACCAGCG TAGCCCCGAT GTAAGCTTGT TGCATGGGCG
GCCTCGATAC GATTGGTCGC ATCGGGGCTA CATTGAACA ACGTACCCGC

33601 GCGATATAAA ATGCAAGGTG CTGCTCAAAA AATCAGGCAA AGCCTCGCGC
CGCTATATTT TACGTTCCAC GACGAGTTTT TTAGTCCGTT TCGGAGCGCG

33651 AAAAAAGAAA GCACATCGTA GTCATGCTCA TGCAGATAAA GGCAGGTAAG
TTTTTCTTTT CGTGTAGCAT CAGTACGAGT ACGTCTATTT CCGTCCATTC

33701 CTCCGGAACC ACCACAGAAA AAGACACCAT TTTCTCTCA AACATGTCTG
GAGGCCCTTG TGGTGTCTTT TTCTGTGGTA AAAAGAGAGT TTGTACAGAC

33751 CGGGTTTCTG CATAAACACA AAATAAAATA ACAAAAAAAC ATTTAAACAT
GCCCAAAGAC GTATTTGTGT TTTATTTTAT TGTTTTTTTG TAAATTTGTA

33801 TAGAAGCCTG TCTTACAACA GGAAAAACAA CCCTTATAAG CATAAGACGG
ATCTTCGGAC AGAATGTTGT CCTTTTGTGTT GGAATATTG GTATTCTGCC

33851 ACTACGGCCA TGCCGGCGTG ACCGTAAAAA AACTGGTCAC CGTGATTAAA
TGATGCCGGT ACGGCCGCAC TGGCATTTTT TTGACCAGTG GCACTAATTT

33901 AAGCACCACC GACAGCTCCT CGGTCAATGC CGGAGTCATA ATGTAAGACT
TTCGTGGTGG CTGTCGAGGA GCCAGTACAG GCCTCAGTAT TACATTCTGA

33951 CGGTAAACAC ATCAGGTTGA TTCACATCGG TCAGTGCTAA AAAGCGACCG
GCCATTTGTG TAGTCCAAC TAAAGTAGCC AGTCACGATT TTTCGCTGGC

34001 AAATAGCCCG GGGGAATACA TACCCGCGAG CGTAGAGACA ACATTACAGC
TTTATCGGGC CCCCTTATGT ATGGGCGTCC GCATCTCTGT TGTAAATGTCG

34051 CCCCATAGGA GGTATAACAA AATTAATAGG AGAGAAAAAC ACATAAACAC
GGGGTATCCT CCATATTGTT TTAATTATCC TCTCTTTTTG TGTATTTGTG

Figure 27A J

34151 ACATACAGCG CTTCCACAGC GGCAGCCATA ACAGTCAGCC TTACCAGTAA
 TGTATGTCGC GAAGGTGTCG CCGTCGGTAT TGTCAGTCGG AATGGTCATT

 34201 AAAAGAAAAC CTATTA AAAA AACACCACTC GACACGGCAC CAGCTCAATC
 TTTTCTTTTG GATAATTTT TTGTGGTGAG CTGTGCCGTG GTCGAGTTAG

 34251 AGTCACAGTG TAAAAAAGGG CCAAGTGCAG AGCGAGTATA TATAGGACTA
 TCAGTGTAC ATTTTTTCCC GGTTCACGTC TCGCTCATAT ATATCCTGAT

 34301 AAAAATGACG TAACGGTTAA AGTCCACAAA AAACACCCAG AAAACCGCAC
 TTTTACTGCG ATTGCCAATT TCAGGTGTTT TTTGTGGGTC TTTTGGCGTG

 34351 GCGAACCTAC GCCCAGAAAC GAAAGCCAAA AAACCCACAA CTTCTCATA
 CGCTTGATG CGGGTCTTTG CTTTCGGTTT TTTGGGTGTT GAAGGAGTTT

 34401 TCGTCACTTC CGTTTTCCCA CGTTACGTCA CTTCCCATT TAAGAAACT
 AGCAGTGAAG GCAAAAGGGT GCAATGCAGT GAAGGGTAAA ATTCTTTTGA

 34451 ACAATTCCCA ACACATACAA GTTACTCCGC CCTAAACCT ACGTCACCCG
 TGTAAAGGGT TGTGTATGTT CAATGAGGCG GGATTTTGA TGCAGTGGCG

 34501 CCCCCTTCCC ACGCCCCGCG CCACGTCACA AACTCCACCC CCTCATTATC
 GGGGCAAGGG TCGGGGCGC GGTGCAGTGT TTGAGGTGGG GGAGTAATAG

PacI

 34551 ATATTGGCTT CAATCCAAAA TAAGGTATAT TATTGATGAT GTTAATTAAG
 TATAACCGAA GTTAGGTTTT ATTCCATATA ATAACCTACTA CAATTAATTC

 34601 AATTCGGATC TGCACGCGA GGCTGGATGG CCTTCCCAT TATGATTCTT
 TTAAGCCTAG ACGCTGCGCT CCGACCTACC GGAAGGGGTA ATACTAAGAA

 34651 CTCGCTTCCG GCGGCATCGG GATGCCCGCG TTGCAGGCCA TGCTGTCCAG
 GAGCGAAGGC CGCCGTAGCC CTACGGGCGC AACGTCCGGT ACGACAGGTC

 34701 GCAGGTAGAT GACGACCATC AGGGACAGCT TCAAGGCCAG CAAAAGGCCA
 CGTCCATCTA CTGCTGGTAG TCCCTGTGCA AGTTCCGGTC GTTTTCCGGT

 34751 GGAACCGTAA AAAGGCCGCG TTGCTGGCGT TTTTCCATAG GCTCCGCCCC
 CCTTGGCATT TTCCGGCGC AACGACCGCA AAAAGGTATC CGAGGCGGGG

 34801 CCTGACGAGC ATCACAAAAA TCGACGCTCA AGTCAGAGGT GGCGAAACCC
 GGACTGCTCG TAGTGTTTTT AGCTGCCAGT TCAGTCTCCA CCGCTTTGGG

 34851 GACAGGACTA TAAAGATACC AGGCGTTTCC CCCTGGAAGC TCCCTCGTGC
 CTGTCTGAT ATTTCTATGG TCCGCAAAGG GGGACCTTCG AGGGAGCAGC

 34901 GCTCTCCTGT TCCGACCCTG CCGCTTACCG GATACCTGTC CGCCTTTCTC
 CGAGAGGACA AGGCTGGGAC GGCGAATGGC CTATGGACAG GCGGAAAGAG

 34951 CCTTCGGGAA GCGTGGCGCT TTCTCATAGC TCACGCTGTA GGTATCTCAG
 GGAAGCCCTT CGCACC CGA AAGAGTATCG AGTGCACAT CCATAGAGTC

 35001 TTCGGTGTAG GTCGTTGCT CCAAGCTGGG CTGTGTGCAC GAACCCCCCG
 AAGCCACATC CAGCAAGCGA GGTTCGACCC GACACACGTG CTGCGGGGGC

Figure 27 AK

AAGTCGGGCT GGCACGCGG AATAGGCCAT TGATAGCAGA ACTCAGGTTG

35101 CCGTAAGAC ACGACTTATC GCCACTGGCA GCAGCCACTG GTAACAGGAT
GGCCATTCTG TGCTGAATAG CGGTGACCGT CGTCGGTGAC CATTGTCCTA

35151 TAGCAGAGCG AGGTATGTAG GCGGTGCTAC AGAGTTCTTG AAGTGGTGGC
ATCGTCTCGC TCCATACATC CGCCACGATG TCTCAAGAAC TTCACCACCG

35201 CTAACACGG CTACACTAGA AGGACAGTAT TTGGTATCTG CGCTCTGCTG
GATTGATGCC GATGTGATCT TCCTGTCATA AACCATAGAC GCGAGACGAC

35251 AAGCCAGTTA CCTTCGGAAA AAGAGTTGGT AGCTCTTGAT CCGGCAACA
TTCGGTCAAT GGAAGCCTT TTCTCAACCA TCGAGAACTA GGCCGTTTGT

35301 AACCACCGCT GGTAGCGGTG GTTTTTTTGT TTGCAAGCAG CAGATTACGC
TTGGTGGCGA CCATCGCCAC CAAAAAACA AACGTTCGTC GTCTAATGCG

35351 GCAGAAAAA AGGATCTCAA GAAGATCCTT TGATCTTTTC TACGGGGTCT
CGTCTTTTTT TCCTAGAGTT CTTCTAGGAA ACTAGAAAAG ATGCCCCAGA

35401 GACGCTCAGT GGAACGAAAA CTCACGTAA GGGATTTTGG TCATGAGATT
CTGCGAGTCA CCTTGCTTTT GAGTGCAATT CCCTAAAACC AGTACTCTAA

35451 ATCAAAAAGG ATCTTCACCT AGATCCTTTT AAATCAATCT AAAGTATATA
TAGTTTTTCC TAGAAGTGA TCTAGGAAAA TTTAGTTAGA TTTTCATATAT

35501 TGAGTAACT TGGTCTGACA GTTACCAATG CTTAATCAGT GAGGCACCTA
ACTCATTTGA ACCAGACTGT CAATGGTTAC GAATTAGTCA CTCCGTGGAT

35551 TCTCAGCGAT CTGTCTATTT CGTTCATCCA TAGTTGCCTG ACTCCCCGTC
AGAGTCGCTA GACAGATAAA GCAAGTAGGT ATCAACGGAC TGAGGGGCGA

35601 GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC CCAGTGCTGC
CACATCTATT GATGCTATGC CCTCCCGAAT GGTAGACCGG GGTCACGACG

35651 AATGATACCG CGAGACCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA
TTACTATGGC GCTCTGGGTG CGAGTGCCG AGGTCTAAAT AGTCGTATT

35701 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC
TGGTCGGTCG GCCTTCCCGG CTCGCGTCTT CACCAGGACG TTGAAATAGG

35751 GCCTCCATCC AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC
CGGAGGTAGG TCAGATAATT AACAACGGCC CTTGATCTC ATTCATCAAG

35801 GCCAGTTAAT AGTTTGCGCA ACGTTGTTGC CATTGCTACA GGCATCGTGG
CGGTCAATTA TCAAACGCGT TGCAACAACG GTAACGATGT CCGTAGCACC

35851 TGTACGCTC GTCGTTTGGT ATGGCTTCAT TCAGCTCCGG TTCCCAACGA
ACAGTGCGAG CAGCAAACCA TACCGAAGTA AGTCGAGGCC AAGGGTTGCT

35901 TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAG CGGTTAGCTC
AGTTCGCTC AATGTACTAG GGGGTACAAC ACGTTTTTTC GCCAATCGAG

35951 CTTGGTCCT CCGATCGTTG TCAGAAGTAA GTTGCCGCA GTGTTATCAC
GAAGCCAGGA GGCTAGCAAC AGTCTTCATT CAACCGGCGT CACAATAGTG

Figure 2 AL

36051 AGATGCTTTT CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA
 TCTACGAAAA GACACTGACC ACTCATGAGT TGGTTCAGTA AGACTCTTAT
 36101 GTGTATGCGG CGACCGAGTT GCTCTTGCCC GCGGTCAACA CGGGATAATA
 CACATACGCC GCTGGCTCAA CGAGAACGGG CCGCAGTTGT GCCCTATTAT
 36151 CCGCGCCACA TAGCAGAACT TTAAAAGTGC TCATCATTGG AAAACGTTCT
 GGCGCGGTGT ATCGTCTTGA AATTTTCACG AGTAGTAACC TTTTGCAAGA
 36201 TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT CCAGTTCGAT
 AGCCCCGCTT TTGAGAGTTC CTAGAATGGC GACAACTCTA GGTCAGCTA
 36251 GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA
 CATTGGGTGA GCACGTGGGT TGA CTAGATAAG TCGTAGAAAA TGAAAGTGGT
 36301 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA
 CGCAAAGACC CACTCGTTTT TGTCTTCCG TTTTACGGCG TTTTTCCTT
 36351 ATAAGGGCGA CACGGAATG TTGAATACTC ATACTCTTCC TTTTCAATA
 TATTCCTGCT GTGCCTTAC AACTTATGAG TATGAGAAGG AAAAAGTTAT
 36401 TTATTGAAGC ATTTATCAGG GTTATTGTCT CATGAGCGGA TACATATTTG
 AATAACTTCG TAAATAGTCC CAATAACAGA GTACTCGCCT ATGTATAAAC
 36451 AATGTATTTA GAAAAATAAA CAAATAGGGG TTCGCGCAC ATTTCCCCGA
 TTACATAAAT CTTTTTATTT GTTTATCCCC AAGGCGCGTG TAAAGGGGCT
 36501 AAAGTGCCAC CTGACGTCTA AGAAACCATT ATTATCATGA CATTAACCTA
 TTTCACGGTG GACTGCAGAT TCTTTGGTAA TAATAGTACT GTAATTGGAT
 36551 TAAAAATAGG CGTATCACGA GGCCCTTTTCG TCTTCAAGAA TTGGATCCGA
 ATTTTATCC GCATAGTGCT CCGGGAAGC AGAAGTCTT AACCTAGGCT

PacI

36601 ATTCTTAATT TCTTAATTAA (SEQ ID NO:34)
 TAAGAATTAA AGAATTAATT (SEQ ID NO:35)

Figure 27AM

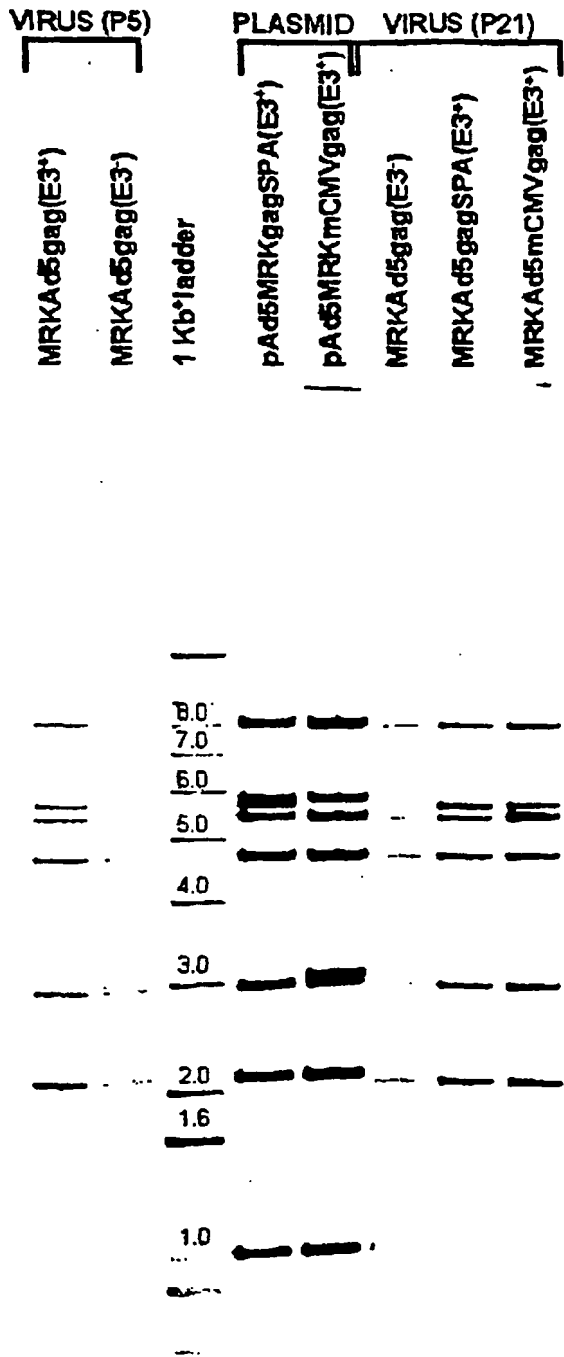


FIGURE 28

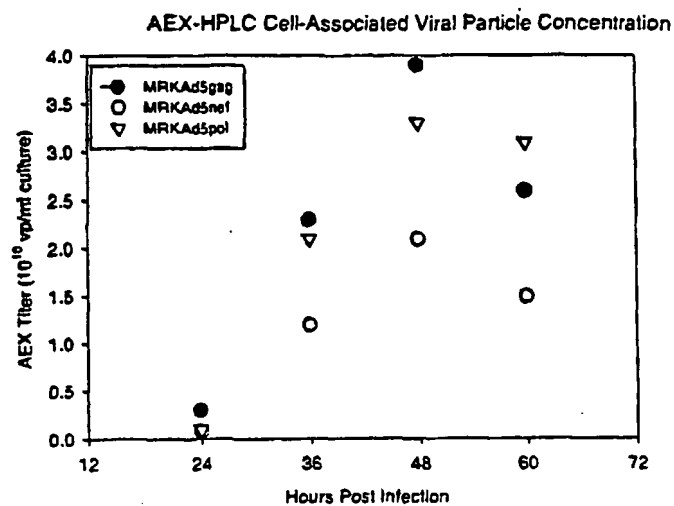


FIGURE 29A

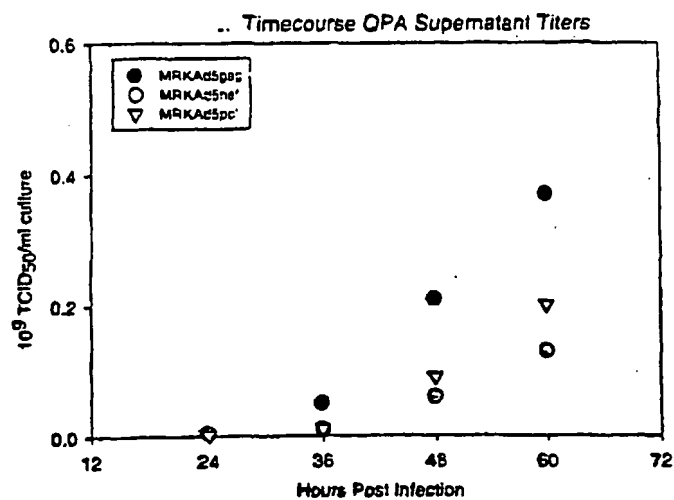


FIGURE 29B

atg gat gca atg aag aga ggg ctc tgc tgt gtg ctg ctg ctg tgt gga Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly 1 5 10 15	48
gca gtc ttc gtt tgc ccc agc gag atc tcc att gtg tgg gcc tcc agg Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ile Val Trp Ala Ser Arg 20 25 30	96
gag ctg gag agg ttt gct gtg aac cct ggc ctg ctg gag acc tct gag Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser Glu 35 40 45	144
ggg tgc agg cag atc ctg ggc cag ctc cag ccc tcc ctg caa aca ggc Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly 50 55 60	192
tct gag gag ctg agg tcc ctg tac aac aca gtg gct acc ctg tac tgt Ser Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys 65 70 75 80	240
gtg cac cag aag att gat gtg aag gac acc aag gag gcc ctg gag aag Val His Gln Lys Ile Asp Val Lys Asp Thr Lys Glu Ala Leu Glu Lys 85 90 95	288
att gag gag gag cag aac aag tcc aag aag aag gcc cag cag gct gct Ile Glu Glu Glu Gln Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala 100 105 110	336
gct ggc aca ggc aac tcc agc cag gtg tcc cag aac tac ccc att gtg Ala Gly Thr Gly Asn Ser Ser Gln Val Ser Gln Asn Tyr Pro Ile Val 115 120 125	384
cag aac ctc cag ggc cag atg gtg cac cag gcc atc tcc ccc cgg acc Gln Asn Leu Gln Gly Gln Met Val His Gln Ala Ile Ser Pro Arg Thr 130 135 140	432
ctg aat gcc tgg gtg aag gtg gtg gag gag aag gcc ttc tcc cct gag Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys Ala Phe Ser Pro Glu 145 150 155 160	480
gtg atc ccc atg ttc tct gcc ctg tct gag ggt gcc acc ccc cag gac Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr Pro Gln Asp 165 170 175	528
ctg aac acc atg ctg aac aca gtg ggg ggc cat cag gct gcc atg cag Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met Gln 180 185 190	576
atg ctg aag gag acc atc aat gag gag gct gct gag tgg gac agg ctg Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Leu 195 200 205	624
cat cct gtg cac gct ggc ccc att gcc ccc ggc cag atg agg gag ccc His Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro 210 215 220	672
agg ggc tct gac att gct ggc acc acc tcc acc ctc cag gag cag att Arg Gly Ser Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile 225 230 235 240	720
ggc tgg atg acc aac aac ccc ccc atc cct gtg ggg gaa atc tac aag Gly Trp Met Thr Asn Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys 245 250 255	768

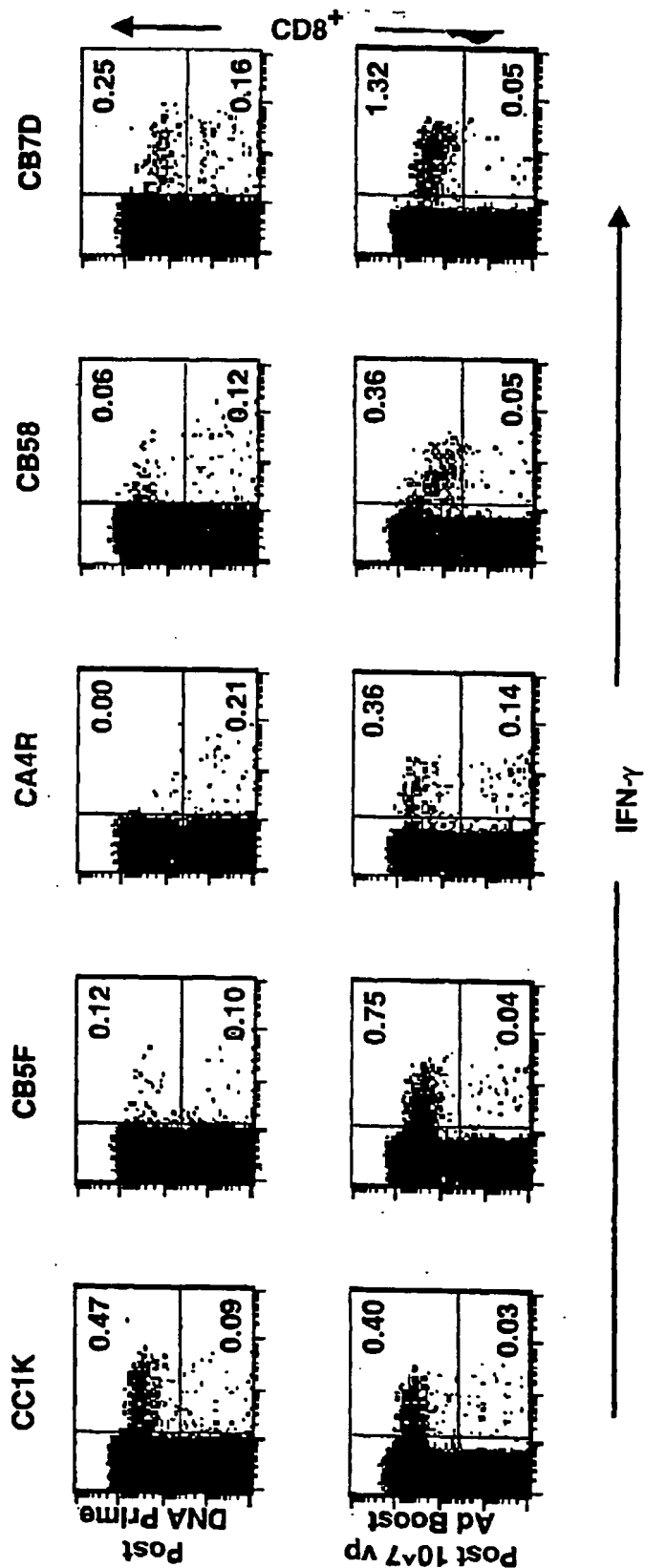
Figure 30A

agg tgg atc atc ctg ggc ctg aac aag att gtg agg atg tac tcc ccc Arg Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg Met Tyr Ser Pro 260 265 270	816
acc tcc atc ctg gac atc agg cag ggc ccc aag gag ccc ttc agg gac Thr Ser Ile Leu Asp Ile Arg Gln Gly Pro Lys Glu Pro Phe Arg Asp 275 280 285	864
tat gtg gac agg ttc tac aag acc ctg agg gct gag cag gcc tcc cag Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala Glu Gln Ala Ser Gln 290 295 300	912
gag gtg aag aac tgg atg aca gag acc ctg ctg gtg cag aat gcc aac Glu Val Lys Asn Trp Met Thr Glu Thr Leu Val Gln Asn Ala Asn 305 310 315 320	960
cct gac tgc aag acc atc ctg aag gcc ctg ggc cct gct gcc acc ctg Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr Leu 325 330 335	1008
gag gag atg atg aca gcc tgc cag ggg gtg ggg ggc cct ggt cac aag Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys 340 345 350	1056
gcc agg gtg ctg gct gag gcc atg tcc cag gtg acc aac tcc gcc acc Ala Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Ser Ala Thr 355 360 365	1104
atc atg atg cag agg ggc aac ttc agg aac cag agg aag aca gtg aag Ile Met Met Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Thr Val Lys 370 375 380	1152
tgc ttc aac tgt ggc aag gtg ggc cac att gcc aag aac tgt agg gcc Cys Phe Asn Cys Gly Lys Val Gly His Ile Ala Lys Asn Cys Arg Ala 385 390 395 400	1200
ccc agg aag aag ggc tgc tgg aag tgt ggc aag gag ggc cac cag atg Pro Arg Lys Lys Gly Cys Trp Lys Cys Gly Lys Glu Gly His Gln Met 405 410 415	1248
aag gac tgc aat gag agg cag gcc aac ttc ctg ggc aaa atc tgg ccc Lys Asp Cys Asn Glu Arg Gln Ala Asn Phe Leu Gly Lys Ile Trp Pro 420 425 430	1296
tcc cac aag ggc agg cct ggc aac ttc ctc cag tcc agg cct gag ccc Ser His Lys Gly Arg Pro Gly Asn Phe Leu Gln Ser Arg Pro Glu Pro 435 440 445	1344
aca gcc cct ccc gag gag tcc ttc agg ttt ggg gag gag aag acc acc Thr Ala Pro Pro Glu Glu Ser Phe Arg Phe Gly Glu Glu Lys Thr Thr 450 455 460	1392
ccc agc cag aag cag gag ccc att gac aag gag ctg tac ccc ctg gcc Pro Ser Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu Ala 465 470 475 480	1440
tcc ctg agg tcc ctg ttt ggc aac gac ccc tcc tcc cag taa (SID NO:36) 1482 Ser Leu Arg Ser Leu Phe Gly Asn Asp Pro Ser Ser Gln * (SID NO:37) 485 490	

Figure 30 B

Figure 31

IFN- γ Secretion against Gag 20-aa pool from CD3⁺ T cells of Monkey PBMCs



Comparison of Single-Modality Adenovirus Immunization with DNA+Adjuvant Prime/Adenovirus Boost

Immunizations

DNA-CRL1005 Prime/Ad Boost

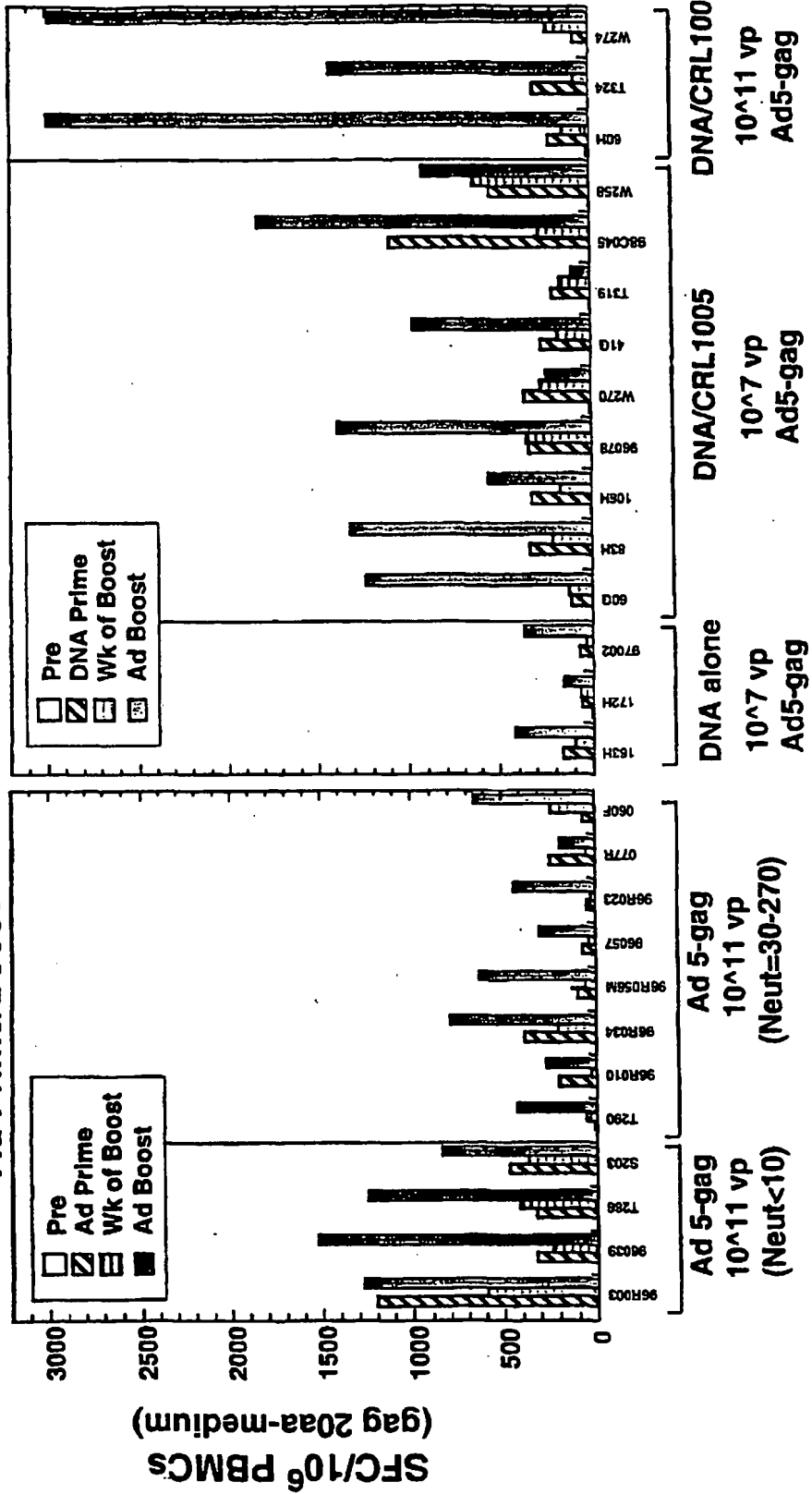


FIGURE 33A

ATGGGTGCTA GGGCTTCTGT GCTGTCTGGT GGTGAGCTGG ACAAGTGGGA GAAGATCAGG
 CTGAGGCCTG GTGGCAAGAA GAAGTACAAG CTAAAGCACA TTGTGTGGGC CTCCAGGGAG
 CTGGAGAGGT TTGCTGTGAA CCCTGGCCTG CTGGAGACCT CTGAGGGGTG CAGGCAGATC
 CTGGGCCAGC TCCAGCCCTC CCTGCAAACA GGCTCTGAGG AGCTGAGGTC CCTGTACAAC
 ACAGTGGCTA CCCTGTACTG TGTGCACCAG AAGATTGATG TGAAGGACAC CAAGGAGGCC
 CTGGAGAAGA TTGAGGAGGA GCAGAACAAG TCCAAGAAGA AGGCCAGCA GGCTGCTGCT
 GGCACAGSCA ACTCCAGCCA GGTGTCCAG AACTACCCCA TTGTGCAGAA CCTCCAGGGC
 CAGATGGTGC ACCAGGCCAT CTCCCCCGG ACCCTGAATG CCTGGGTGAA GGTGGTGGAG
 GAGAAGGCCT TCTCCCTGTA GGTGATCCCC ATGTTCTCTG CCCTGTCTGA GGGTGCCACC
 CCCCAGGACC TGAACACCAT GCTGAACACA GTGGGGGGCC ATCAGGCTGC CATGCAGATG
 CTGAAGGAGA CCATCAATGA GGAGGCTGCT GAGTGGGACA GGCTGCATCC TGTGCACGCT
 GGCCCCATTG CCCCCGGCCA GATGAGGGAG CCCAGGGGCT CTGACATTGC TGGCACCACC
 TCCACCCTCC AGGAGCAGAT TGGCTGGATG ACCAACAACC CCCCATCCC TGTGGGGGAA
 ATCTACAAGA GGTGGATCAT CCTGGGCCTG AACAGATTG TGAGGATGTA CTCCCCACC
 TCCATCCTGG ACATCAGGCA GGGCCCCAAG GAGCCCTTCA GGGACTATGT GGACAGGTTT
 TACAAGACCC TGAGGGCTGA GCAGGCCTCC CAGGAGGTGA AGAACTGGAT GACAGAGACC
 CTGCTGGTGC AGAATGCCAA CCCTGACTGC AAGACCATCC TGAAGGCCCT GGGCCCTGCT
 GCCACCCTGG AGGAGATGAT GACAGCCTGC CAGGGGGTGG GGGGCCCTGG TCACAAGGCC
 AGGGTGCTGG CTGAGGCCAT GTCCAGGTG ACCAACTCCG CCACCATCAT GATGCAGAGG
 GGCAACTTCA GGAACCAGAG GAAGACAGTG AAGTGCTTCA ACTGTGGCAA GGTGGGCCAC
 ATGCAAGA ACTGTAGGGC CCCCAGGAAG AAGGGCTGCT GGAAGTGTGG CAAGGAGGGC
 CACCAGATGA AGGACTGCAA TGAGAGGCAG GCCAACTTCC TGGGCAAAAT CTGGCCCTCC
 CACAAGGGCA GGCCTGGCAA CTTCTCCAG TCCAGGCCTG AGCCACAGC CCCTCCCGAG
 GAGTCCTTCA GGTTTGGGGA GGAGAAGACC ACCCCAGCC AGAAGCAGGA GCCCATGAC
 AAGGAGCTGT ACCCCCTGGC CTCCCTGAGG TCCCTGTTTG GCAACGACCC CTCCTCCAG
 ATGGCTCCCA TCTCCCCCAT TGAGACTGTG CCTGTGAAGC TGAAGCCTGG CATGGATGGC
 CCCAAGGTGA AGCAGTGGCC CCTGACTGAG GAGAAGATCA AGGCCCTGGT GGAAATCTGC
 ACTGAGATGG AGAAGGAGGG CAAAATCTCC AAGATTGGCC CCGAGAACCC CTACAACACC
 CCTGTGTTTG CCATCAAGAA GAAGGACTCC ACCAAGTGA GGAAGCTGGT GGACTTCAGG
 GAGCTGAACA AGAGGACCCA GGAATTCTGG GAGGTGCAGC TGGGCATCCC CCACCCCGCT
 GGCTGAAGA AGAAGAAGTC TGTGACTGTG CTGGCTGTGG GGGATGCCTA CTTCTCTGTG
 CCCCCTGGATG AGGACTTCAG GAAGTACACT GCCTTCACCA TCCCCTCCAT CAACAATGAG
 ACCCCTGGCA TCAGGTACCA GTACAATGTG CTGCCCCAGG GCTGGAAGGG CTCCCCTGCC
 ATCTTCCAGT CCTCCATGAC CAAGATCCTG GAGCCCTTCA GGAAGCAGAA CCCTGACATT
 GTGATCTACC AGTACATGGC TGCCCTGTAT GTGGGCTCTG ACCTGGAGAT TGGGCAGCAC
 AGGACCAAGA TTGAGGAGCT GAGGCAGCAC CTGCTGAGGT GGGGCCTGAC CACCCCTGAC
 AAGAAGCACC AGAAGGAGCC CCCCTTCTG TGGATGGGCT ATGAGCTGCA CCCCAGACAAG
 TGGACTGTGC AGCCCATTTG GCTGCCCTGAG AAGGACTCCT GGACTGTGAA TGACATCCAG
 AAGCTGGTGG GCAAGCTGAA CTGGGCCTCC CAAATCTACC CTGGCATCAA GGTGAGGCAG
 CTGTGCAAGC TGCTGAGGGG CACCAAGGCC CTGACTGAGG TGATCCCCCT GACTGAGGAG
 GCTGAGCTGG AGCTGGCTGA GAACAGGGAG ATCCTGAAGG AGCCTGTGCA TGGGGTGTAC

FIGURE 33B

TATGACCCCT CCAAGGACCT GATTGCTGAG ATCCAGAAGC AGGGCCAGGG CCAGTGGACC
TACCAAATCT ACCAGGAGCC CTTCAAGAAC CTGAAGACTG GCAAGTATGC CAGGATGAGG
GGGGCCCACA CCAATGATGT GAAGCAGCTG ACTGAGGCTG TGCAGAAGAT CACCACTGAG
TCCATTGTGA TCTGGGGCAA GACCCCAAG TTCAAGCTGC CCATCCAGAA GGAGACCTGG
GAGACCTGGT GGA CTGAGTA CTGGCAGGCC ACCTGGATCC CTGAGTGGGA GTTGTGAAC
ACCCCCCCCC TGGTGAAGCT GTGGTACCAG CTGGAGAAGG AGCCCATTTGT GGGGGCTGAG
ACCTTCTATG TGGCTGGGGC TGCCAACAGG GAGACCAAGC TGGGCAAGGC TGGCTATGTG
ACCAACAGGG GCAGGCAGAA GGTGGTGACC CTGACTGACA CCACCAACCA GAAGACTGCC
CTCCAGGCCA TCTACCTGGC CCTCCAGGAC TCTGGCCTGG AGGTGAACAT TGTGACTGCC
TCCAGTATG CCCTGGGCAT CATCCAGGCC CAGCCTGATC AGTCTGAGTC TGAGCTGGTG
AACCAGATCA TTGAGCAGCT GATCAAGAAG GAGAAGGTGT ACCTGGCCTG GGTGCCTGCC
CACAAGGGCA TTGGGGGCAA TGAGCAGGTG GACAAGCTGG TGTCTGCTGG CATCAGGAAG
GTGCTGTTCC TGGATGGCAT TGACAAGGCC CAGGATGAGC ATGAGAAGTA CCACTCCAAC
TGGAGGGGTA TGGCCTCTGA CTTCAACCTG CCCCCTGTGG TGGCTAAGGA GATTGTGGCC
TCCTGTGACA AGTGCCAGCT GAAGGGGGAG GCCATGCATG GGCAGGTGGA CTGCTCCCTT
GGCATCTGGC AGCTGGCCTG CACCCACCTG GAGGGCAAGG TGATCCTGGT GGCTGTGCAT
GTGGCCTCCG GCTACATTGA GGCTGAGGTG ATCCCTGCTG AGACAGGCCA GGAGACTGCC
TACTTCCTGC TGAAGCTGGC TGGCAGGTGG CCTGTGAAGA CCATCCACAC TGCCAATGGC
TCCAATTCA CTGGGGCCAC AGTGAGGGCT GCCTGCTGGT GGGCTGGCAT CAAGCAGGAG
TTTGGCATCC CCTACAACCC CCAGTCCCAG GGGGTGGTGG CCTCCATGAA CAAGGAGCTG
AAGAAGATCA TTGGGCAGGT GAGGGACCAG GCTGAGCACC TGAAGACAGC TGTGCAGATG
GCTGTGTTCA TCCACAACCT CAAGAGGAAG GGGGGCATCG GGGGCTACTC CGCTGGGGAG
AGGATTGTGG ACATCATTGC CACAGACATC CAGACCAAGG AGCTCCAGAA GCAGATCACC
AAGATCCAGA ACTTCAGGGT GTACTACAGG GACTCCAGGA ACCCCCTGTG GAAGGGCCCT
GCCAAGCTGC TGTGGAAGGG GGAGGGGGCT GTGGTGATCC AGGACAACCTC TGACATCAAG
GTGGTGCCCA GGAGGAAGGC CAAGATCATC AGGGACTATG GCAAGCAGAT GGCTGGGGAT
GACTGTGTGG CCTCCAGGCA GGATGAGGAC TAA
SEQ ID NO: 38

FIGURE 34A

Met Gly Ala Arg Ala Ser Val Leu Ser Gly Gly Glu Leu Asp Lys Trp Glu Lys
 Ile Arg Leu Arg Pro Gly Gly Lys Lys Lys Tyr Lys Leu Lys His Ile Val Trp
 Ala Ser Arg Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser
 Glu Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly Ser
 Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys Val His Gln
 Lys Ile Asp Val Lys Asp Thr Lys Glu Ala Leu Glu Lys Ile Glu Glu Glu Gln
 Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala Ala Gly Thr Gly Asn Ser Ser
 Gln Val Ser Gln Asn Tyr Pro Ile Val Gln Asn Leu Gln Gly Gln Met Val His
 Gln Ala Ile Ser Pro Arg Thr Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys
 Ala Phe Ser Pro Glu Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr
 Pro Gln Asp Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met
 Gln Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Leu His
 Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro Arg Gly Ser
 Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile Gly Trp Met Thr Asn
 Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys Arg Trp Ile Ile Leu Gly Leu
 Asn Lys Ile Val Arg Met Tyr Ser Pro Thr Ser Ile Leu Asp Ile Arg Gln Gly
 Pro Lys Glu Pro Phe Arg Asp Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala
 Glu Gln Ala Ser Gln Glu Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln
 Asn Ala Asn Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr
 Leu Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys Ala
 Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Ser Ala Thr Ile Met Met
 Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Thr Val Lys Cys Phe Asn Cys Gly
 Lys Val Gly His Ile Ala Lys Asn Cys Arg Ala Pro Arg Lys Lys Gly Cys Trp
 Lys Cys Gly Lys Glu Gly His Gln Met Lys Asp Cys Asn Glu Arg Gln Ala Asn
 Phe Leu Gly Lys Ile Trp Pro Ser His Lys Gly Arg Pro Gly Asn Phe Leu Gln
 Ser Arg Pro Glu Pro Thr Ala Pro Pro Glu Glu Ser Phe Arg Phe Gly Glu Glu
 Lys Thr Thr Pro Ser Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu
 Ala Ser Leu Arg Ser Leu Phe Gly Asn Asp Pro Ser Ser Gln Met Ala Pro Ile
 Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys
 Val Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile Cys
 Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr
 Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu
 Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu
 Gly Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Ala
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr
 Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr
 Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met
 Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr Gln
 Tyr Met Ala Ala Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr
 Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp
 Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro

FIGURE 34B

Asp Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val
Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro
Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr
Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu
Ile Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu Ile
Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu
Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr
Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile
Val Ile Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp
Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe
Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile
Val Gly Ala Glu Thr Phe Tyr Val Ala Gly Ala Ala Asn Arg Glu Thr Lys Leu
Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu Thr
Asp Thr Thr Asn Gln Lys Thr Ala Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp
Ser Gly Leu Glu Val Asn Ile Val Thr Ala Ser Gln Tyr Ala Leu Gly Ile Ile
Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln
Leu Ile Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile
Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu
Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn
Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile
Val Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln Val
Asp Cys Ser Pro Gly Ile Trp Gln Leu Ala Cys Thr His Leu Glu Gly Lys Val
Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro
Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp
Pro Val Lys Thr Ile His Thr Ala Asn Gly Ser Asn Phe Thr Gly Ala Thr Val
Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn
Pro Gln Ser Gln Gly Val Val Ala Ser Met Asn Lys Glu Leu Lys Lys Ile Ile
Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val
Phe Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly Glu
Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln
Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu
Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln
Asp Asn Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp
Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp
SEQ ID NO: 39

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/86
 US CL : 435/456

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/205.1, 207.1, 227.1, 233.1; 435/69.1, 69.3, 173.3, 235.1, 320.1, 456; 530/23.72;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 96/39178 (ERTL et al.) 12 December 1996 (12.12.1996), see page 5, 6, 10, 12, 13 and claims 1 and 5.	1-3, 8-11, 18 ----- 4, 5, 13-17, 29-32, 34, 35, 37
X --- Y	US 6,019,978 A (ERTL et al.) 1 February 2000 (01/02/2000), see columns 2, 7 and 8.	1-3, 8-11, 18 ----- 4, 5, 13-17, 29-32, 34, 35, 37
X,P	US 6,287,571 B1 (ERTL et al.) 11 September 2001 (11/09/2001), see columns 2, 7, 8 and claim 1.	1, 9, 18
X --- Y	US 5,643,579A (HUNG et al.) 1 July 1997 (01/07/1997), see examples 1, 2, 25 and 26.	1-3, 8, 9-11, 18 ----- 4,5,13-17, 29-32, 34, 35, 37
Y	WANG et al. The use of an E1-deleted, replication -defective adenovirus recombinant expressing the rabies virus glycoprotein for early vaccination of mice against rabies virus. Journal of Virology (March 1997) Vol. 71, No. 5, pp 3677-3683.	1-3, 9-11, 13-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

06 February 2002 (06.02.2002)

Date of mailing of the international search report

19 AUG 2002

Name and mailing address of the ISA/US

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 Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Ulrike Winkler, Ph.D.

Telephone No. 703-308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/28861

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NATUK et al. Immunogenicity of recombinant human adenovirus -human immunodeficiency virus vaccines in chimpanzees. Aids Research and Human Retroviruses (1993) Vol. 9, No. 5, pp395-404, see material and methods.	1, 9, 29-32
Y	PREVEC et al. Immune response to HIV-1 gag antigens induced by recombinant adenovirus vectors in mice and rhesus macaque monkeys. Journal of Acquired Immune Deficiency Syndrome. (1991) Vol. 4, No. 6 pp. 568-76, see abstract.	1, 9, 29-32
Y	LORI et al. Rapid protection against human immunodeficiency virus type 1 (HIV-1) replication mediated by high efficiency non-retroviral delivery of genes interfering with HIV-1 tat and gag. Gene Therapy (1994) Vol. 1, No. 1, pp. 27-31, see abstract.	1, 9
Y	PFARR et al. Differential effects of polyadenylation regions on gene expression in mammalian cells. DNA (1986) Vol. 5, No. 2, pp.115-22, see abstract.	16
Y	NATUK et al. Adenovirus vectored vaccine. Developmental Biological Standards (1994) Vol. 82, pp. 71-77, see abstract.	1, 9

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5, 8-11, 13-18, 29-32, 34, 35, 37

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group	Claims	
1	1-5, 8-11, 13-18, 29, 30, 31, 32, 34, 35, 37	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Gag protein (SEQ ID NO: 29) inserted in the parallel orientation of E1. In addition the vector contains a promoter and a polyadenylation signal.
2	6, 7, 36	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> and <u>ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Gag protein (SEQ ID NO: 29).
3	12, 33	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV protein inserted in the antiparallel orientation of E1.
4	19-23, 38-42	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Gag protein.
5	24, 27, 28, 43, 46, 47	The claim is directed to a method of generating a cellular mediated immune response to HIV Gag protein with the recombinant adenoviral particle.
6	25, 26, 44, 45	The claim is directed to a method of generating a cellular mediated immune response to HIV Gag protein with the recombinant adenoviral particle in addition to administering a DNA plasmid vaccine.
7	48-51, 53, 54, 56	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 1) inserted in the parallel orientation of E1.
8	48-51, 53, 54, 56	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 5) inserted in the parallel orientation of E1.
9	48-51, 53, 54, 56	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 7) inserted in the parallel orientation of E1.
10	52	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 1) inserted in the antiparallel orientation of E1.
11	52	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 5) inserted in the antiparallel orientation of E1.
12	52	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 7) inserted in the antiparallel orientation of E1.
13	55	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u>

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		and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 1) inserted in E1.
14	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 5) inserted in E1.
15	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 7) inserted in E1.
16	57-61	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Pol protein.
17	62, 65, 66	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle.
18	63, 64	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle in addition to administering a DNA plasmid vaccine.
19	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the parallel orientation of E1.
20	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the parallel orientation of E1.
21	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the parallel orientation of E1.
22	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the parallel orientation of E1.
23	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the antiparallel orientation of E1.
24	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the antiparallel orientation of E1.
25	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the antiparallel orientation of E1.
26	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the antiparallel orientation of E1.
27	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in E1.
28	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in E1.
29	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$, the vector contains the cis-acting packaging sequence of the wild type

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		adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in E1.
30	74	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1 and ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in E1.
31	76-80	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Nef protein.
32	81, 84, 85	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle.
33	82, 83	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle in addition to administering a DNA plasmid vaccine.
34	86a	The claim is drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from three individual vectors.
35	86b, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from one individual vectors.
36	86c, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-pol</i> fusion and one expressing <i>gag</i> .
37	86d, 87, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>gag-pol</i> fusion and one expressing <i>nef</i> .
38	86e, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-gag</i> fusion and one expressing <i>pol</i> .
39	86f, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from a single vectors as a fusion protein.
40	86g, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed from two individual vectors.
41	86h, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed individually from one vector.
42	86i, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from two individual vectors.
43	86j, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from individually from one vector.
44	86k, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
45	86l, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
46	86m, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed as a fusion protein from one vector.
47	86n, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed as a fusion protein from one vector.
48	86o, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed as a fusion protein from one vector.

The inventions listed as Groups 1-48 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups 1-33 appears to be a recombinant adenoviral vector wherein the adenoviral vector is at least partially deleted in E1 but the vector may contain more deletions, the vector contains wild type sequences including packaging signals and a gene encoding a heterologous HIV protein or fragments thereof. Erd et al. (WO 96/39178) disclose a recombinant adenoviral vector that is deleted in E1 and partially deleted in E3, the remainder of the adenoviral vector contains wild type sequences. The vector additionally contains an insertion of a heterologous protein which includes HIV proteins (see abstract and claims 1 and 5). Therefore, the technical feature linking the inventions of groups 1-45 does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of the following groups 1-3, 7-15, 19-30 and 34-48 is considered to be the combination of sequences that is disclosed in each group, see individual claim groupings above for the different sequences. The DNA disclosed in each group is made up of a different sequence having a different structure and different function.

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The special technical feature of group 4, 16 and 31 is considered to be a method of producing recombinant adenoviral particles. Each group contains different sequences hence the resulting particles would have different structures and functions associated with the particle.

The special technical feature of group 5, 17 and 32 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors. Each group contains different sequences encoding different protein, therefore the resulting immune response will also be different.

The special technical feature of group 6, 18 and 33 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors in conjunction with immunizing the individual a DNA plasmid vaccine. Each method contains different sequences encoding a different protein, therefore the resulting immune response will also be different.

Accordingly, groups 1-48 are not so linked by the same or corresponding technical feature as to form a single general inventive concept.

Continuation of B. FIELDS SEARCHED Item 3:

WEST 2.0, STN-BIOSIS, MEDLINE

adenoviral vector, deletion, HIV, Gag, polyadenylation signal, CMV promoter